10/757,059

=> d his

(FILE 'HOME' ENTERED AT 08:33:05 ON 23 AUG 2004)

FILE 'CAPLUS' ENTERED AT 08:33:17 ON 23 AUG 2004
L1 76706 S ATPASE
L2 18443 S K ATPASE

FILE 'REGISTRY' ENTERED AT 08:34:50 ON 23 AUG 2004
E PANTOPRAZOLE/CN
L3 1 S E3

FILE 'CAPLUS' ENTERED AT 08:35:24 ON 23 AUG 2004
L4 64 S L3 AND L2
L5 0 S BIB ABS 1-64

=> d l4 bib abs 1-64

L4 ANSWER 1 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:522109 CAPLUS
DN 141:82049
TI Pantoprazole treatment does not invoke anti-inflammatory properties in vivo
AU Becker, Tagliane Liza; Marostica, Marta; Ribeiro, Marcelo Lima; de Mendonca, Sergio; Gambero, Alessandra; Pedrazzoli, Jose
CS Clinical Pharmacology and Gastroenterology Unit, Sao Francisco University Medical School, Sao Paulo, 12916-900, Brazil
SO International Immunopharmacology (2004), 4(8), 1051-1057
CODEN: IINMBA; ISSN: 1567-5769
PB Elsevier Science B.V.
DT Journal
LA English
AB Background and aims: Proton pump inhibitors (PPIs) are antiulcer agents that have gastric antisecretory and mucosal protective actions. The antisecretory effect of these agents derives from the inhibition of gastric parietal cell proton pump H+/**K+ ATPase**. The exact mechanism of PPI-induced gastric mucosal protection is not known though. It has been suggested that PPI may accumulate, modulating the functions of neutrophils and, thus, may be useful in reducing the gastric mucosal injury caused by these cells. However, these same mechanisms may not be desirable when PPIs are prescribed in prophylaxis and pre-operatively for ill or immunodepressed patients. The present study was designed to examine a possible anti-neutrophil activity of pantoprazole in vivo. A short study with omeprazole and lansoprazole was also performed. Methods: Dosages of PPIs able to inhibit basal acid secretion (10 and 100 mg kg-1) were administered i.p. (i.p.) to rats for 7 or 28 days. Cimetidine (100 mg kg-1) and dexamethasone (0.75 mg kg-1) were used as controls for antisecretory and anti-inflammatory activity, resp. Air pouches were then developed in these animals, and Helicobacter pylori suspension or carrageenan was used as inflammatory stimulus. Exudate formation and leukocyte migration to air pouches were assessed. Results: Neither short nor long treatment with pantoprazole modified the ability of neutrophils to migrate in response to carrageenan or H. pylori. The same results were obtained when omeprazole or lansoprazole was used. Dexamethasone, alone, a potent anti-inflammatory drug, was able to reduce polymorphonuclear and mononuclear cell migration. Conclusion: Based on these observations, pantoprazole and other PPIs seem to have no anti-inflammatory properties in vivo.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

10/757,059

AN 2004:453656 CAPLUS
DN 141:116452
TI Chemistry of Covalent Inhibition of the Gastric (H+, **K**+)-**ATPase** by Proton Pump Inhibitors
AU Shin, Jai Moo; Cho, Young Moon; Sachs, George
CS Department of Physiology and Medicine, University of California, Los Angeles, CA, 90073, USA
SO Journal of the American Chemical Society (2004), 126(25), 7800-7811
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Proton pump inhibitors (PPIs), drugs that are widely used for treatment of acid related diseases, are either substituted pyridylmethylsulfinyl benzimidazole or imidazopyridine derivs. They are all prodrugs that inhibit the acid-secreting gastric (H+, **K**+)-**ATPase** by acid activation to reactive thiophiles that form disulfide bonds with one or more cysteines accessible from the exoplasmic surface of the enzyme. This unique acid-catalysis mechanism had been ascribed to the nucleophilicity of the pyridine ring. However, the data obtained here show that their conversion to the reactive cationic thiophilic sulfenic acid or sulfenamide depends mainly not on pyridine protonation but on a second protonation of the imidazole component that increases the electrophilicity of the C-2 position on the imidazole. This protonation results in reaction of the C-2 with the unprotonated fraction of the pyridine ring to form the reactive derivs. The relevant PPI pKa's were determined by UV spectroscopy of the benzimidazole or imidazopyridine sulfinylmethyl moieties at different medium pH. Synthesis of a relatively acid stable analog, N1-Me lansoprazole, allowed direct determination of both pKa values of this intact PPI allowing calcn. of the two pKa values for all the PPIs. These values predict their relative acid stability and thus the rate of reaction with cysteines of the active proton pump at the pH of the secreting parietal cell. The PPI accumulates in the secretory canaliculus of the parietal cell due to pyridine protonation then binds to the pump and is activated by the second protonation on the surface of the protein to allow disulfide formation.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:72648 CAPLUS
DN 141:81442
TI Clinical pharmacology of proton pump inhibitors: what the practicing physician needs to know
AU Robinson, Malcolm; Horn, John
CS Department of Medicine, Oklahoma Foundation for Digestive Research, University of Oklahoma College of Medicine, Oklahoma City, OK, USA
SO Drugs (2003), 63(24), 2739-2754
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. Proton pump inhibitors (PPIs) [omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole] are widely utilized for the treatment of gastro-esophageal reflux disease, as well as other acid-related disorders. All PPIs suppress gastric acid secretion by blocking the gastric acid pump, H+/**K**+-**ATPase**, but the physicochem. properties of these drugs result in variations in the degree of acid suppression, as well as the speed of onset of acid inhibition. Such differences may impact on the clin. performance of PPIs, and this manuscript discusses data that may help clinicians choose between the

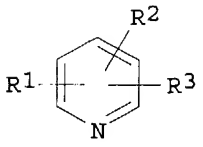
available PPIs for specific clin. situations and indications. The characteristics of PPIs that have been developed subsequent to omeprazole offer several advantages over this prototype PPI, particularly with respect to the onset of acid suppression and reduced potential for inter-individual pharmacokinetic variation and drug interactions. Newer agents inhibit H+/**K**+-**ATPase** more rapidly than omeprazole and emerging clin. data support potential clin. benefits resulting from this pharmacol. property. Although key pharmacokinetic parameters (time to maximum plasma concentration and elimination half-life) do not differ significantly among PPIs, differences in the hepatic metabolism of these drugs can produce inter-patient variability in acid suppression, in the potential for pharmacokinetic drug interactions and, quite possibly, in clin. efficacy. All PPIs undergo significant hepatic metabolism Because there is no direct toxicity from PPIs, there is minimal risk from the administration of any of them - even to patients with significant renal or hepatic impairment. However, there are significant genetic polymorphisms for one of the cytochrome P 450 (CYP) isoenzymes involved in PPI metabolism (CYP2C19), and this polymorphism has been shown to substantially increase plasma levels of omeprazole, lansoprazole and pantoprazole, but not those of rabeprazole. Hepatic metabolism is also a key determinant of the potential for a given drug to be involved in clin. significant pharmacokinetic drug interactions. Omeprazole has the highest risk for such interactions among PPIs, and rabeprazole and pantoprazole appear to have the lowest risk. Thus, whereas all PPIs have been shown to be generally effective and safely used for the treatment of acid-mediated disorders, there are chemical, pharmacodynamic and pharmacokinetic differences among these drugs that may make certain ones more, or less, suitable for treating different patient subgroups. Of course, the absolute magnitude of risk from any PPI in terms of drug-drug interactions is probably low - excepting interactions occurring as class effects related to acid suppression (e.g. increased digoxin absorption or inability to absorb ketoconazole).

RE.CNT 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

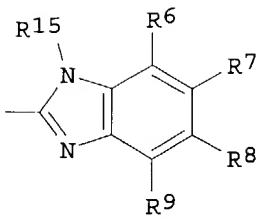
L4 ANSWER 4 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:348788 CAPLUS
DN 138:353993
TI Preparation of benzimidazole derivatives as prodrugs of proton pump inhibitors
IN Garst, Michael E.; Sachs, George; Shin, Jai Moo
PA Regents of the University of California, USA; The United States Department of Veteran Affairs; Winston Pharmaceuticals, LLC
SO U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 364,381, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6559167	B1	20030506	US 2001-783807	20010214
	US 6093734	A	20000725	US 1998-131481	19980810
	TR 200100431	T2	20010621	TR 2001-200100431	19990809
	ES 2192394	T3	20031001	ES 1999-942057	19990809
	RU 2232159	C2	20040710	RU 2001-123313	19990809
	ZA 2001000560	A	20010713	ZA 2001-560	20010119
PRAI	US 1998-131481	A2	19980810		
	US 1999-364381	B2	19990729		
	RU 2001-107009	A	19990809		

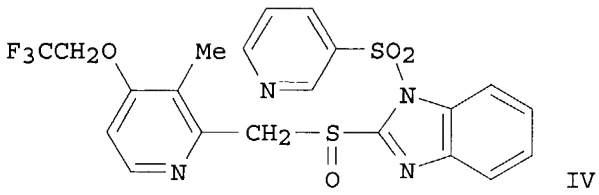
OS MARPAT 138:353993
GI



II



III



IV

AB The title compds. Het1XSOHet2 [I; Het1 = II; X = CHR10; Het2 = III; R1-R3 = H, alkyl, fluoroalkyl, etc.; R6-R9 = H, alkyl, haloalkyl, etc.; R10 = H, alkyl; R15 = SO2R21(R17); R17 = alkyl, haloalkyl, alkoxy, etc.; R21 = (un)substituted aralkyl, heteroarylalkyl] which are prodrugs of the pyridyl Me sulfinyl benzimidazole type proton pump inhibitor drugs having a hydrolyzable arylsulfonyl or heteroarylsulfonyl group attached to the benzimidazole nitrogen, were prepared Thus, reacting 2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)-1H-benzimidazole with pyridine-3-sulfonyl chloride in the presence of Et3N in CH2Cl2 afforded the title compound IV. The prodrugs I hydrolyze under physiol. conditions to provide the proton pump inhibitors with a half life measurable in hours, and are capable of providing sustained plasma concns. of the proton pump inhibitor drugs for longer time than presently used drugs. The generation of the proton pump inhibitor drugs from the prodrugs of the invention (I) under physiol. conditions allows for more effective treatment of several diseases and conditions caused by gastric acid secretion (e.g., ulcers). Biol. data for compds. I were given.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:321973 CAPLUS
DN 139:316299
TI Synthesis or rupture: duration of acid inhibition by proton pump inhibitors
AU Sachs, G.; Shin, J. M.; Pratha, V.; Hogan, D.
CS Membrane Biology Laboratory, University of California, Los Angeles, CA, USA
SO Drugs of Today (2003), 39(Suppl. A, Pantoprazole), 11-14
CODEN: MDACAP; ISSN: 0025-7656
PB Prous Science
DT Journal; General Review
LA English
AB A review. Insight has been gained into the relationship between the structure of proton pump inhibitors (PPIs), their binding, and their suppression of acid secretion. PPIs accumulate in the acidic space of the secreting parietal cell, where then their active forms create disulfide bonds with key cysteines of the H+,**K+-ATPase**. Studies

in humans on the half-lives of recovery of acid secretion have found that while lansoprazole showed a half-life of less than 15 h, and both omeprazole and rabeprazole showed one of less than 30 h, for pantoprazole the half-life was approx. 46 h. This difference in duration of inhibition with PPIs may be related to variations in proton pump inhibitor dwell time. A study in rats suggests that the recovery of gastric pump activity after treatment with omeprazole, esomeprazole, lansoprazole and rabeprazole is likely due to both reversal of binding by disulfide-reducing agents and to pump synthesis. However, for pantoprazole, reversal of acid inhibition is probably due mainly to de novo pump synthesis and not loss of binding. This profile is likely related to the unique binding of pantoprazole to cysteine 822, a binding site which is buried deep within the membrane domain of the pump and may therefore be inaccessible to reducing agents. Although clin. data supporting these findings are limited, prolonged binding of pantoprazole may confer a longer duration of action in comparison with other PPIs.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:249790 CAPLUS
DN 139:159401
TI Differential drug-induced mRNA expression of human CYP3A4 compared to CYP3A5, CYP3A7 and CYP3A43
AU Krusekopf, Solveigh; Roots, Ivar; Kleeberg, Ullrich
CS Charite, Institute of Clinical Pharmacology, Humboldt University of Berlin, Berlin, D-10098, Germany
SO European Journal of Pharmacology (2003), 466(1-2), 7-12
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB Drug-mediated regulation of mRNA expression of all members of the cytochrome P 450 3A (CYP3A) subfamily has been measured by reverse transcription-polymerase chain reaction (RT-PCR) in the human hepatocellular carcinoma cell line, HepG2. Transcriptional regulation was proved by inhibition of induction with actinomycin D. Besides the pos. control dexamethasone, the H/**K**-**ATPase** inhibitors omeprazole, lansoprazole, pantoprazole, and rabeprazole, and the herbal antidepressant St. John's wort (Hypericum extract) were studied. All CYP3A mRNAs were induced by dexamethasone. CYP3A4 was the only CYP3A isoform that was induced by all of the four benzimidazole derivs., while CYP3A5, CYP3A7, and CYP3A43 were unaffected or even slightly downregulated by these drugs. St. John's wort also increased CYP3A4 mRNA exclusively, leaving CYP3A5 and CYP3A43 unaffected, whereas CYP3A7 was decreased. Depending on the inducer, expression of CYP3A4 is differently regulated from CYP3A5, CYP3A7, and CYP3A43.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:203783 CAPLUS
DN 139:95407
TI Time-dependent transcriptional induction of CYP1A1, CYP1A2 and CYP1B1 mRNAs by H+/**K**+-**ATPase** inhibitors and other xenobiotics
AU Krusekopf, S.; Roots, I.; Hildebrandt, A. G.; Kleeberg, U.
CS Institute of Clinical Pharmacology, Humboldt University of Berlin, Berlin, D-10098, Germany
SO Xenobiotica (2003), 33(2), 107-118
CODEN: XENOBH; ISSN: 0049-8254
PB Taylor & Francis Ltd.
DT Journal

LA English
AB Xenobiotic-mediated regulation of mRNA expression of all members of the human cytochrome P 450 (CYP) 1 family has been measured by RT-PCR in the hepatoma cell line, HepG2. Besides the pos. control β-naphthoflavone, the H+/**K+-ATPase** inhibitors omeprazole, lansoprazole, pantoprazole and rabeprazole and the anti-malaria drug primaquine were included in this study. β-Naphthoflavone, primaquine, omeprazole and lansoprazole increased mRNA levels of CYP1A1, CYP1A2 and CYP1B1. Induction by rabeprazole was significant only for CYP1A1 and CYP1A2, whereas none of the CYP1 mRNAs was induced by pantoprazole. This result was confirmed in primary human hepatocytes. Transcriptional regulation was proved by inhibition of induction with actinomycin D. Increase of CYP1 mRNA was significant after 1 h and maximal after 4 h. CYP1B1, but not CYP1A1 or CYP1A2, was dramatically down-regulated between 4 and 24 h. This decrease was prevented by treatment of cells with actinomycin D after induction, indicating an active transcription-dependent mechanism of CYP1B1 mRNA degradation In conclusion, xenobiotics inducing CYP1A1 mRNA expression have been shown also to induce CYP1A2 and CYP1B1, differing only with regard to level and time course of induction.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:905038 CAPLUS
DN 139:63026
TI Restoration of acid secretion following treatment with proton pump inhibitors
AU Shin, Jai Moo; Sachs, George
CS Department of Physiology and Medicine, University of California at Los Angeles, and VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
SO Gastroenterology (2002), 123(5), 1588-1597
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Background& Aims: Proton pump inhibitors (PPIs) are covalent inhibitors of the gastric H+,**K+-ATPase** (ATPase) forming disulfide bonds. Recovery of acid secretion after PPI inhibition may be, due to de novo synthesis of pump protein and/or disulfide reduction and reactivation of inhibited pump. The halftime of recovery of acid secretion in rats following omeprazole treatment is .apprx.15 h, whereas pump protein half-life is 54 h. In humans, the half-life of the inhibitory effect on acid secretion is .apprx.28 h for omeprazole and .apprx.46 h for pantoprazole. Whereas all PPIs bind to cysteine 813, pantoprazole addnl. binds to cysteine 822, deeper in the membrane domain of TM6. Their different durations of action may reflect different rates of pump reactivation due to differing accessibility of the disulfides to glutathione. Methods: Rats were stimulated and treated with 30 mg/kg of each PPI. Gastric ATPase was prepared and reversal of inhibition of the H+, **K+-ATPase** was measured as the time-dependent restoration of activity by incubation with dithiothreitol or glutathione. Results: One hundred percent reactivation of ATPase following inhibition in vivo by omeprazole or its enantiomers was seen with dithiothreitol and 89% with glutathione. Similar data were found for lansoprazole or rabeprazole: No reactivation by either reducing agent was seen following inhibition by pantoprazole. Conclusions: Recovery of acid secretion following inhibition by all PPIs, other than pantoprazole, may depend on both protein turnover and reversal of the inhibitory disulfide bond. In contrast, recovery of acid secretion after pantoprazole may depend entirely on new protein synthesis.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:523096 CAPLUS
DN 137:103273
TI Pharmacology of acid suppression in the hospital setting: Focus on proton pump inhibition
AU Pisegna, Joseph R.
CS Greater Los Angeles Veterans Administration, Los Angeles, CA, USA
SO Critical Care Medicine (2002), 30(6, Suppl.), S356-S361
CODEN: CCMDC7; ISSN: 0090-3493
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English
AB A review. The more potent and longer-lasting inhibition of gastric acid secretion provided by proton pump inhibitors (PPIs) as compared with histamine-2-receptor antagonists is caused in large part by differences in their mechanism of action. PPIs block histamine-2-, gastrin-, and cholinergic-mediated sources of acid production and inhibit gastric secretion at the final common pathway of the H+/**K+ ATPase** proton pump. In contrast, histamine-2-receptor antagonists cannot block receptor sites other than those mediated by histamine. It seems that the rapid loss of acid suppression activity by the histamine-2-receptor antagonists may be attributed to tolerance. Such tolerance has not occurred in patients receiving PPIs because these agents are irreversible inhibitors of the H+/**K+ ATPase** proton pump. For these reasons, patients who have acid-related disorders that require high levels of acid suppression do not respond well to i.v. histamine-2-receptor antagonists and would be excellent candidates for i.v. PPI therapy. Candidates for i.v. PPIs also include patients who cannot receive oral PPIs and those who may need the higher acid suppression therapy provided by the i.v. rather than the oral route. Clin. studies have demonstrated the efficacy of i.v. pantoprazole in maintaining adequate control of gastric acid output during the switch from oral to i.v. therapy in patients with severe gastroesophageal reflux disease or the Zollinger-Ellison syndrome. Intragastric administration of solns. prepared from oral PPIs has been used as an alternative to the i.v. route in critical care settings. However, decreased bioavailability may limit the value of intragastric delivery of PPIs because of the high frequency of gastric emptying problems in critically ill patients.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:45026 CAPLUS
DN 136:294395
TI Conformational analysis: a new approach by means of chemometrics
AU Bruni, Aline Thais; Leite, Vitor B. P.; Ferreira, Marcia M. C.
CS Instituto de Quimica, Universidade Estadual de Campinas UNICAMP, Campinas, 13083-970, Brazil
SO Journal of Computational Chemistry (2002), 23(2), 222-236
CODEN: JCCHDD; ISSN: 0192-8651
PB John Wiley & Sons, Inc.
DT Journal
LA English
AB In conformational anal., the systematic search method completely maps the space but suffers from the combinatorial explosion problem because the number of conformations increases exponentially with the number of free rotation angles. This study introduces a new methodol. of conformational anal. that controls the combinatorial explosion. It is based on a dimensional reduction of the system through the use of principal component anal. The

results are exactly the same as those obtained for the complete search but, in this case, the number of conformations increases only quadratically with the number of free rotation angles. The method is applied to three drugs; omeprazole, pantoprazole, lansoprazole-benzimidazoles that suppress gastric-acid secretion by H+, **K+-ATPase** enzyme inhibition.

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:818120 CAPLUS
DN 137:41064
TI The relationship between pH-selectivity, chirality, and efficacy of gastric proton pump inhibitors
AU Kromer, Wolfgang
CS Department of Pharmacology, Byk Gulden, Konstanz, D-78467, Germany
SO Current Topics in Pharmacology (2000), 5, 45-69
CODEN: CTPCF5
PB Research Trends
DT Journal; General Review
LA English
AB A review. Gastric proton pump inhibitors (PPIs) are substituted benzimidazole prodrugs. They are converted by acid inside the canaliculus of the parietal cell into a cyclic sulfenamide that immediately reacts with SH-groups of the H+/**K+-ATPase** in a covalent manner. Since only a fraction of parietal cells is in the acid-secreting state at any time of drug administration, the chemical activation half-life of PPIs at pH 1, relative to their serum elimination half-life, will determine their antisecretory effect. No relevant differences in this respect are detectable between the PPIs. In order to avoid unwanted SH reactions in cells apart from the parietal cell, PPIs should be converted into their active principle as slowly as possible at pH values above 3. For example, pH values around 5 are encountered in lysosomes which are affected in their function both, in vitro and ex vivo, by omeprazole. This contrasts to the more pH-selective PPI pantoprazole. Rabeprazole is by far the least pH-selective PPI with a chemical activation half-life at pH 5 in the order of 0.1 h, compared to about 2 h at 37 in the case of pantoprazole. Since all the PPIs have a similar serum elimination half-life of about 1 h (with a wide variation between subjects from 0.5 to 2 h), rabeprazole is expected to be more liable to cause unwanted SH reactions. Actually, incidences of infectious and inflammatory adverse events between 2 and 5 % have been listed in the "Summary of Product Characteristics" of rabeprazole, compared to only 0.12-0.14 % found in clin. studies on pantoprazole. Although these data are derived from different clin. studies, this preliminary comparison between the two PPIs is at least in line with the notion of biol. relevant differences in pH-selectivities of PPIs. As opposed to the prodrugs, the cyclic sulfenamides are achiral and no longer optically active. Consequently, the (S)-enantiomer of omeprazole (esomeprazole) is equieffective compared to the racemate, in terms of pharmacodynamics. Since esomeprazole displays a slightly longer serum elimination half-life than the (R)-enantiomer in extensive metabolizers, it has been claimed to be more effective than the racemate, on a mg basis. However, the racemate already contains 50 % of the (S)-enantiomer, and overall healing rates do not seem to support the above claim. Consequently, esomeprazole's dose for acute healing has been raised from the original dose of 20 mg omeprazole racemate to that dose previously optimal in the development of pantoprazole, namely 40 mg.

RE.CNT 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:752824 CAPLUS

DN 135:314438
TI Proteolipid subunits of vacuolar H+-ATPase (ATP6F) as tumor antigens, application to cancer therapy, and use of proton pump inhibitor as anticancer agent
IN Sato, Nobuo; Suzuki, Nobutaka; Yamaguchi, Masaaki; Yamaguchi, Nobuo; Okuma, Katsuji
PA Japan
SO Jpn. Kokai Tokkyo Koho, 79 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2001286284	A2	20011016	JP 2000-103966	20000405
PRAI	JP 2000-103966		20000405		

AB Proteolipid subunits of vacuolar H+-ATPase (V-ATPase) as tumor antigens, use of antibodies and antisense oligonucleotides targeting those antigens as anticancer agent, and use of proton pump inhibitor as anticancer agent, are disclosed. Tumor antigen recognized by monoclonal antibody KCT-1 was isolated from thyroid cancer cell line TPC-1. The amino acid sequence of this antigen named SSY (S-1) was found match that of vacuolar H+-ATPase proteolipid subunit (ATP6F, c'' subunit). The epitope of SSY antigen for KCT-1 antibody was determined SSY antigen was found to strongly expressed in all the cancers examined; thyroid cancer, breast cancer, stomach cancer, esophagus cancer (squamous cell carcinoma), laryngeal cancer, colon cancer, rectal cancer, anal cancer, pancreatic cancer, lung cancer, renal cancer, bladder cancer, ovarian cancer, uterus cancer, cervical cancer, cunnus cancer, skin cancer, melanoma, central or peripheral nervous system cancer, gingival cancer, pharyngeal carcinoma, mediastinal tumor, liver cancer, bile duct cancer (cholangioma), gallbladder cancer, renal pelvis tumor, ureter cancer, testicular cancer, fallopian tube cancer, vaginal cancer, sarcoma, leukemia, erythroleukemia, multiple myeloma, malignant lymphoma, and carcinosarcoma. CDNA for a mouse homolog was cloned. Intradermal, s.c., and oral administration of the antigen in mouse demonstrated antitumor activity and safety. Antitumor activity was also demonstrated by phosphorothioate antisense oligonucleotide. Various inhibitors of V-ATPase, H+/**K+-ATPase**, and H+/Cl- symporter were found to have antitumor activity.

L4 ANSWER 13 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:475714 CAPLUS
DN 135:282488
TI Pantoprazole
AU Poole, Patricia
CS Department of Pharmaceutical Services, University of California Davis Medical Center, Sacramento, CA, USA
SO American Journal of Health-System Pharmacy (2001), 58(11), 999-1008
CODEN: AHSPEK; ISSN: 1079-2082
PB American Society of Health-System Pharmacists
DT Journal; General Review
LA English
AB A review with 50 refs. The pharmacol., pharmacokinetics, clin. efficacy, adverse effects, and dosage and administration of pantoprazole are reviewed. Pantoprazole is a gastric hydrogen-potassium ATPase (H+/**K+-ATPase**) inhibitor. It shares the same core structure as other currently available proton-pump inhibitors (PPIs). The FDA-labeled indication is the short-term treatment of erosive esophagitis. PPIs act by selectively inhibiting H+/**K+-ATPase** in the secretory canaliculus of the stimulated parietal cell. Understanding the pharmacodynamics of PPIs is more relevant than knowing their pharmacokinetics, since the duration of action depends on the rate of de

novo proton-pump regeneration, not the duration of drug circulation in the body. Pantoprazole is well absorbed, undergoes little first-pass metabolism, and has an absolute bioavailability of approx. 77%. Pantoprazole has been evaluated in more than 100 clin. trials involving more than 11,000 patients. It is effective in treating erosive esophagitis and duodenal and gastric ulcers. It is also effective as adjunctive treatment with antimicrobials in patients infected with Helicobacter pylori. Pantoprazole has been shown to control acid production in Zollinger-Ellison syndrome. Pantoprazole is well tolerated. The most commonly reported adverse effects are headache, diarrhea, and abdominal pain. The recommended oral dosage for erosive esophagitis is 40 mg once a day for up to eight weeks. The recommended i.v. dose is 40 mg given over 15 min once a day in patients with gastroesophageal reflux disease who are unable to take oral medication. Pantoprazole appears to be as safe and effective as other PPIs in acid-related disorders.

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:450876 CAPLUS
DN 135:51076
TI New stable multi-unitary pharmaceutical preparations containing substituted benzimidazoles
IN Goncalves Mendes, Carla Patricia; Caeiro Ramalho De Oliveira, Maria Julia
PA Laboratorio Medinfar-Produtos Farmaceuticos, S.A., Port.
SO Eur. Pat. Appl., 28 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1108425	A1	20010620	EP 1999-670010	19991216
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 6379705	B1	20020430	US 2000-580551	20000530
PRAI	EP 1999-670010	A	19991216		

AB The present invention relates to new oral multi-unitary pharmaceutical prepns. containing substituted benzimidazoles as inhibitors of H+,**K**+-**ATPase** (i.e., omeprazole, lansoprazole, pantoprazole, leminoprazole and pariprazole) or their pharmaceutically acceptable salts. Such pharmaceutical prepns. are stable pellet prepns. containing substituted benzimidazole(s) or their salts and they comprise a quantity of active ingredient of 1-50 mg, an inert core of spherical symmetry with a diameter of 600-1000 μm, constituted by inert excipients, coated with an active layer containing at least one substituted benzimidazole in the micronized form and various pharmaceutically acceptable inert excipients, mixed in suitable proportions in order to allow the disaggregation of the formulations and dissoln. of the active ingredient(s) in an appropriate manner, coated in turn with an insulating layer of a polymer soluble in water, free from alkaline and/or alkaline-earthy metallic salts, of a min. thickness of 15 μm, this layer being coated lastly with a gastro-resistant or enteric layer of a min. thickness of 30 μm. This invention also refers to the process for the preparation of said pharmaceutical prepns.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:902374 CAPLUS
DN 135:101662
TI Pantoprazole: A new proton pump inhibitor

AU Jungnickel, Paul W.
CS School of Pharmacy, Auburn University, Auburn University, AL, USA
SO Clinical Therapeutics (2000), 22(11), 1268-1293
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica, Inc.
DT Journal; General Review
LA English
AB A review with 104 refs. This paper reviews the pharmacol., clin. efficacy, and tolerability of pantoprazole in comparison with those of other available proton pump inhibitors (PPIs). Relevant English-language research and review articles were identified by data-base searches of MEDLINE, International Pharmaceutical Abstrs., and UnCover, and by examining the reference lists of the articles so identified. In selecting data for inclusion, the author gave preference to full-length articles published in peer-reviewed journals. Like other PPIs, pantoprazole exerts its pharmacodynamic actions by binding to the proton pump (H+,**K**+-**ATPase**) in the parietal cells, but, compared with other PPIs, its binding may be more specific for the proton pump. Pantoprazole is well absorbed when administered as an enteric-coated, delayed-release tablet, with an oral bioavailability of .apprx.77%. It is hepatically metabolized via cytochrome P2C19 to hydroxypantoprazole, an inactive metabolite that subsequently undergoes sulfate conjugation. The elimination half-life ranges from 0.9 to 1.9 h and is independent of dose. Pantoprazole has similar efficacy to other PPIs in the healing of gastric and duodenal ulcers, as well as erosive esophagitis, and as part of triple-drug regimens for the eradication of Helicobacter pylori from the gastric mucosa. It is well tolerated, with the most common adverse effects being headache, diarrhea, flatulence, and abdominal pain. In clin. studies, it has been shown to have no interactions with various other agents, including carbamazepine, cisapride, cyclosporine, digoxin, phenytoin, theophylline, and warfarin. Pantoprazole appears to be as effective as other PPIs. Its low potential for drug interactions may give it an advantage in patients taking other drugs.
RE.CNT 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:626784 CAPLUS
DN 134:95322
TI Drugs used for the control of gastric acidity and the treatment of peptic ulcer
AU Breggia, M. Eugenia; Miguenz, Marcela; Silberman, Palbo E.; Laudisi, Claudia; Lemberg, Abraham; Filinger, Esther
CS Residencia en Farmacia Clinica, Hospital de Clinicas "Jose de San Martin", Buenos Aires, Argent.
SO Acta Farmaceutica Bonaerense (2000), 19(2), 133-142
CODEN: AFBODJ; ISSN: 0326-2383
PB Colegio de Farmaceuticos de la Provincia de Buenos Aires
DT Journal
LA Spanish
AB Differences between H+/**K+ ATPase** inhibitors and histamine H2-receptor antagonists were analyzed, including pharmacokinetic uses in different gastrointestinal pathologies, the administration and adult dosage, as well as pediatric and geriatric dosages, adverse reactions, precautions and drug interactions of the following groups of drugs: (I) Cimetidine, Ranitidine, Famotidine and Nizatidine, and (II) Omeprazole, Lansoprazole, Pantoprazole and Rabeprazole. Addnl., a pharmacoeconomic study of both groups of gastrointestinal drugs has been included.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:420958 CAPLUS
DN 133:48897
TI Pharmaceutical formulations containing prostaglandin analogs and calcium channel blockers and ATPase inhibitors
IN Eek, Arne; Josefsson, Lars; Lundberg, Per Johan; Pilbrant, Ake
PA Astrazeneca AB, Swed.
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000035448	A1	20000622	WO 1999-SE2315	19991210
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000020186	A5	20000703	AU 2000-20186	19991210
	BR 9916224	A	20010904	BR 1999-16224	19991210
	EP 1150677	A1	20011107	EP 1999-963820	19991210
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002532425	T2	20021002	JP 2000-587768	19991210
	NZ 511999	A	20021025	NZ 1999-511999	19991210
	NO 2001002915	A	20010813	NO 2001-2915	20010613
PRAI	SE 1998-4314	A	19981214		
	WO 1999-SE2315	W	19991210		

AB This invention is related to new oral pharmaceutical dosage forms comprising a proton pump inhibitor, i.e. a H+, **K+** - **ATPase** inhibitor, a gastric antisecretory prostaglandin analog, and optionally an addnl. drug such as a calcium channel blocker, especially for use in the treatment and prophylaxis of gastrointestinal disorders. More specifically the invention is related to new dosage forms comprising omeprazole and misoprostol. The invention is also related to a combination of the 3 categories of drugs, i.e., the H+, **K+** - **ATPase** inhibitors, the gastric antisecretory prostaglandin analogs, and the calcium channel blockers. The invention also refers to a method for the manufacture of the described dosage forms and their uses in medicine, as well as blister packs comprising these drugs. Extended-release granules were prepared from misoprostol 0.4, felodipine 10, Cremophor RH-40 10, EtOH 400, HPMC 400, and sodiumstearyl fumarate 4%. Two-layer tablets contained misoprostol 400 μg, felodipine 10, and omeprazole 20 mg and these tablets were coated with a solution of HPMC and PEG having pigments dispersed therein.

L4 ANSWER 18 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:287997 CAPLUS
DN 133:171679
TI The proton-pump inhibitors: similarities and differences
AU Horn, John
CS University of Washington School of Pharmacy, Seattle, WA, USA
SO Clinical Therapeutics (2000), 22(3), 266-280
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica, Inc.
DT Journal; General Review

LA English
AB A review with 52 refs. Objective: This paper examines the clin. pharmacol. of the proton-pump inhibitors (PPIs) and briefly reviews some comparative studies of these agents. Background: PPIs have emerged as the treatment of choice for acid-related diseases, including gastroesophageal reflux disease (GERD) and peptic ulcer disease. Although these drugs,omeprazole, lansoprazole, pantoprazole, and rabeprazole-share a common structure (all are substituted benzimidazoles) and mode of action (inhibition of H+,**K**+-**ATPase** [ATPase]), each differs somewhat in its clin. pharmacol. Results: In comparative clin. trials found in MEDLINE, PPIs administered once daily produced endoscopic evidence of healing in >90% of patients with duodenal ulcer after 4 wk of treatment, in >90% of those with gastric ulcer after 6 wk of treatment, and in >90% of those with ulcerative or erosive GERD after 8 wk of treatment. Maintenance therapy with daily doses of a PPI has been shown to be an effective means of preventing GERD relapse. PPIs also inhibit the growth of Helicobacter pylori, now recognized as an important factor in peptic ulcer disease, and, when administered in combination with antibiotics, provide the best treatment for eradication of the bacterium. Rabeprazole has a more rapid onset of H+,**K**+-**ATPase** inhibition than the other PPIs and, compared with omeprazole, a greater effect on intragastric pH after the first dose. Omeprazole and lansoprazole have a greater potential for drug-drug interactions than do pantoprazole and rabeprazole. Conclusion: Although the individual PPIs have similar efficacy in many cases, differences between them should be considered when choosing a treatment regimen.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:262857 CAPLUS
DN 133:159800
TI Comparison of five antisecretory agents acting via gastric H+/**K**+-**ATPase**
AU Bastaki, Salim M. A.; Chandranath, Irwin; Garner, Andrew
CS Department of Pharmacology, UAE University, Al Ain, United Arab Emirates
SO Journal of Physiology (Paris) (2000), 94(1), 19-23
CODEN: JHYSEM; ISSN: 0928-4257
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
AB Lansoprazole, pantoprazole, rabeprazole and RO-18-5364 (RO) are new benzimidazole derivs. which rival omeprazole as proton pump inhibitors (PPIs) for treatment of ulcer disease. This study compared the effects of these compds. on acid secretion and determined their relative potencies in relation to their effect on [14C]aminopyrine (AP) accumulation in isolated rabbit gastric glands. Dibutyryl cAMP (stimulant of acid secretion) and Ro 20-1724 (a phosphodiasterase inhibitor) were added to Eppendorf tubes containing the PPIs and AP, and concentration-response curves were prepared for each drug after incubating for 5, 10 and 20 min at 37. All the PPIs inhibited acid secretion as demonstrated by the inhibition of AP accumulation in the isolated gastric glands. Min. inhibition occurred at 0.001 μM for lansoprazole and omeprazole, 0.01 μM for rabeprazole and RO and 0.02 μM for pantoprazole. No differences were observed among the PPIs with regard to the maximum inhibition produced. When the IC50 values were compared, the relative potencies of the drugs were different. Maximum potency was in the order lansoprazole (0.007 μM) > omeprazole (0.012 μM) > rabeprazole (0.018 μM) > RO (0.034 μM) > pantoprazole (0.050 μM). Thus, these PPIs showed different potencies as inhibitors of acid secretion as evident from their IC50 values. Ulcer-healing trials demonstrated comparable efficacy, with a number of studies indicating that

symptom relief was most rapid with pantoprazole and lansoprazole, while lansoprazole appeared to be the most potent in inhibiting AP accumulation in the isolated gastric glands.

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:92849 CAPLUS
DN 133:12208
TI Basic aspects of selectivity of pantoprazole and its pharmacological actions
AU Beil, Winfried; Sewing, Karl-Friedrich; Kromer, Wolfgang
CS Institute of General Pharmacology, Hannover Medical School, Hannover, D-30625, Germany
SO Drugs of Today (1999), 35(10), 753-764
CODEN: MDACAP; ISSN: 0025-7656
PB Prous Science
DT Journal; General Review
LA English
AB A review with 69 refs. Pantoprazole sodium is a substituted benzimidazole derivative which controls acid secretion by inhibition of gastric H+/**K**+-**ATPase**. The prodrug pantoprazole accumulates in the acidic space of the parietal cell where it is converted to the pharmacol. active principle, a thiophilic cyclic sulfenamide. The pH-dependent activation profile, i.e., activation at pH 1 vs. activation at pH 4-6, is more favorable for pantoprazole than for the other proton pump inhibitors (PPIs) currently available. In vitro, pantoprazole interferes less potently than omeprazole with biol. targets not related to gastric acid secretion. The gastric target sites for the pantoprazole sulfenamide are the cysteines 813 and 822 of the catalytic subunit of the H+/**K**+-**ATPase**. In contrast to the sites for omeprazole, the 2 binding sites of pantoprazole are located directly at the proton channel. In rats, dogs and humans, pantoprazole produces marked and prolonged inhibition of both basal and stimulated acid secretion. Overall, its antisecretory potency is equal to that of omeprazole. Antiulcer activity has been demonstrated for pantoprazole in 2 rat models. As seen with H2-receptor antagonists and other PPIs, pantoprazole causes an increase in serum gastrin concentration which reflects the degree of gastric acid inhibition.
Pantoprazole is mainly metabolized by cytochrome P 450 3A4 and 2C19, but displays a lower affinity for these phase I cytochrome P 450 enzymes than omeprazole. In contrast to the latter, pantoprazole is further conjugated with sulfate by the hepatic phase II metabolism These 2 differences may explain why pantoprazole does not interfere with the metabolism of any other drug thus far tested in humans.

RE.CNT 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:795602 CAPLUS
DN 132:35699
TI Multibinding inhibitors of H+**K**+-**ATPase**
IN Meier-davis, Susan; Griffin, John H.; Choi, Seok-Ki
PA Advanced Medicine, Inc., USA
SO PCT Int. Appl., 182 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 31

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9963940	A2	19991216	WO 1999-US12925	19990608

WO 9963940	A3	20010607			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6288234	B1	20010911	US 1999-325662		19990604
CA 2319477	AA	19991216	CA 1999-2319477		19990608
SG 80631	A1	20010522	SG 1999-2719		19990608
EP 1143991	A2	20011017	EP 1999-930182		19990608
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
SG 90053	A1	20020723	SG 1999-2944		19990608
US 6566509	B1	20030520	US 1999-327899		19990608
ZA 2000004086	A	20010810	ZA 2000-4086		20000810
ZA 2000004558	A	20011130	ZA 2000-4558		20000831
ZA 2000004559	A	20020402	ZA 2000-4559		20000831
US 2002028943	A1	20020307	US 2001-760827		20010117
US 2004023290	A1	20040205	US 2002-161279		20020603
US 2003176670	A1	20030918	US 2002-330381		20021227
PRAI US 1998-88448P	P	19980608			
US 1998-93072P	P	19980716			
US 1999-325662	A3	19990604			
US 1999-327899	A1	19990608			
US 1999-328071	B1	19990608			
WO 1999-US12925	W	19990608			
US 2000-502938	A1	20000211			

AB Disclosed are multibinding compds., LpXq [where L = a ligand which is an inhibitor of H+/**K+-ATPase**; X = a linker; p = 2-10; q = 1-20], which inhibit H+/**K+-ATPase**, an enzyme which is involved in the control of acid secretion in the stomach. Combinatorial arrays, methods of synthesis, and methods of assaying the dimeric and multimeric compds. are also embodied by the invention. A number of divalent prophetic examples, derived from substituted benzimidazoles and difunctional linkers, are given. The multibinding compds. of this invention are useful in the treatment gastroesophageal reflux disease (GERD) and peptic ulcer disease (no data). The multibinding compds. provide greater biol. and/or therapeutic effects than the aggregate of the unlinked ligands due to their multibinding properties (no data). H+/**K+-ATPase** inhibitor ligands include omeprazole, (S)-omeprazole, pantoprazole, (S)-pantoprazole, lansoprazole, (S)-lansoprazole, rabeprazole,leminoprazole, IY-81149, RO-18-5364, AD-8240, Sch 28080, H-33525, SK&F-97574,SK&F-96067, and YH1885.

L4 ANSWER 22 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:584567 CAPLUS
DN 131:208366
TI Drug interactions with agents used to treat acid-related diseases
AU Humphries, T. J.; Merritt, G. J.
CS Eisai Ltd, London, W6 8EE, UK
SO Alimentary Pharmacology and Therapeutics (1999), 13(Suppl. 3), 18-26
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal; General Review
LA English
AB A review with 69 refs. Patients with acid-related diseases often need to take multiple medications. Treatment of Helicobacter pylori infection often includes either a histamine type 2 (H2)-receptor antagonist or a

proton pump (H+,**K+-ATPase**) inhibitor (proton pump inhibitor), administered in conjunction with one or more antimicrobials. Also, treatment for acid-related diseases often requires extended therapy during which many concomitant medications may be administered for concurrent disease states. Polypharmacy may be the result, particularly in elderly patients, who are at increased risk for both acid-related and many other diseases. Thus, it is important to understand the potential for clin. significant drug-drug interactions in this setting. H2-receptor antagonists and proton pump inhibitors can influence the pharmacokinetic profiles of other commonly administered medications by elevating intragastric pH, which can alter drug absorption, and by interacting with the cytochrome P (CYP) 450 enzyme system, which can affect drug metabolism and clearance. Such interactions are particularly important when they affect the pharmacokinetics of drugs with narrow therapeutic ranges (e.g. warfarin, digoxin). In these cases, drug-drug interactions can result in significant toxicity and even death. There are marked differences among H2-receptor antagonists and proton pump inhibitors in their potential for such interactions. The oldest drugs in each class, cimetidine and omeprazole, resp., have the greatest potential to alter CYP activity and change the pharmacokinetics of other drugs. The most recently developed H2-receptor antagonist, famotidine, and the newer proton pump inhibitors, rabeprazole and pantoprazole, are much less likely to induce or inhibit CYP and thereby change the metabolism of other medications. These differences are important when choosing medications for the safe treatment of patients with acid-related diseases.

RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:561590 CAPLUS
DN 131:184948
TI Preparation of benzimidazolylsulfinylmethylarylamines as (H+/**K+**) **ATPase** inhibitors useful as antiviral agents.
IN Moormann, Alan E.; Becker, Daniel P.; Flynn, Daniel L.; Li, Hui; Villamil, Clara I.
PA G.D. Searle and Co., USA
SO U.S., 54 pp., Cont.-in-part of Ser. No. US 1994-
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5945425	A	19990831	US 1996-737251	19961024
	WO 9529897	A1	19951109	WO 1995-US5021	19950501
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 2001047038	A1	20011129	US 2001-885221	20010620
PRAI	US 1994-235619	B2	19940429		
	WO 1995-US5021	W	19950501		
	US 1996-659098	B1	19960604		
	US 1999-377888	B1	19990819		
	US 2000-605560	B1	20000627		

OS MARPAT 131:184948
AB A method of treating viral infection comprises treatment with R2(CR3R4)pSOm(CR4R5)nR1 [R1 = (substituted) alkoxy, alkoxycarbonyl, dialkylamino, aryl, heteroaryl; R2 = (substituted) heteroaryl; R3-R6 = H,

alkyl, aryl, aralkyl; R3R4, R5R6 = cycloalkyl; m, n, p = 0-2]. Thus, 2-mercaptobenzimidazole and 2-aminobenzyl alc. were heated in HOAc/H2SO4 to give 2-[(1H-benzimidazol-2-yl)thiomethyl]benzeneamine. The latter in CHCl3 was treated with 2-[(1H-benzimidazol-2-yl)sulfinylmethyl]benzeneamin e. Title compds. inhibited HCMV replication with EC50 = 13-61 μM.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:558081 CAPLUS
DN 131:306964
TI Correlation between acid secretion and proton pump activity during inhibition by the proton pump inhibitors omeprazole and pantoprazole
AU Nishioka, K.; Nagao, T.; Urushidani, T.
CS Graduate School of Pharmaceutical Sciences, Laboratory of Pharmacology and Toxicology, The University of Tokyo, Tokyo, Japan
SO Biochemical Pharmacology (1999), 58(8), 1349-1359
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB Omeprazole and pantoprazole are known to be irreversible, SH-acting inhibitors of gastric H+,**K+-ATPase**. Both drugs concentration-dependently and pH-dependently inhibited K+-dependent p-nitrophenyl phosphatase (K+-pNPPase) activity in purified rabbit gastric microsomes. The potency of omeprazole was about three times that of pantoprazole in the pH ranges tested. Both drugs also inhibited acid secretion, as determined by [14C]aminopyrine accumulation in isolated rabbit gastric glands, with the potency ratio being about 5 (omeprazole over that of pantoprazole). Under conditions in which acid secretion was inhibited completely by the drugs, the total K+-pNPPase activity in the digitonin-permeabilized glands was scarcely reduced, showing an apparent discrepancy between the acid secretion and the proton pump activity. The isolated glands were stimulated with secretagogues for 30 min in the presence of the inhibitors, homogenized, and then separated into fractions in which K+-pNPPase activity was measured. Omeprazole exclusively inhibited the activity in the low-speed fraction, which was rich in the apical membranes, whereas pantoprazole did not inhibit activity in any fraction. When the time of treatment with the inhibitors was increased up to 5 h, the inhibition of the total K+-pNPPase activity in the glands reached a plateau at an inhibition rate lower than 50% within 2 h. This suggested that no continuous recycling of the proton pump was occurring during stimulation. The inhibitory effect of both drugs on the permeabilized gland preparation was less potent than that on the purified enzyme, especially at the higher pH, and it appeared to be partially reversible. The extent of the reduction in potency was more prominent for pantoprazole. It is concluded that a lower amount of proton pump activity needs to be inhibited by pantoprazole than by omeprazole to achieve the same extent of acid secretion inhibition. This appears to be due to the nature of pantoprazole, i.e. the requirement of low pH for activation and the partial reversibility of the inhibition.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:502064 CAPLUS
DN 132:117376
TI Studies on H+/**K+-ATPase** inhibitors benzimidazole derivatives
AU Huang, Guobin; Cheng, Maosheng; Huang, Huiqing; Shen, Jianmin
CS Institute of Materia Medica, Shenyang Pharmaceutical University, Shenyang, 110015, Peop. Rep. China

SO Zhongguo Yaowu Huaxue Zazhi (1999), 9(2), 89-93
CODEN: ZYHZEF; ISSN: 1005-0108
PB Zhongguo Yaowu Huaxue Zazhi Bianjibu
DT Journal
LA Chinese
AB Twelve benzimidazole derivs. as H+/**K**+-**ATPase** inhibitors were synthesized and their structures were identified with IR, 1H-NMR and elementary anal. The results of antisecretory activity in vivo tests showed that the compds. 5-isopropylaminoformyl-2-{[(3',4'-dimethoxyl-2'- pyridyl)-methyl]-sulfenyl}-1H-benzimidazole, 5-isopropylaminoformyl-2-{[(3',4'-dimethoxyl-2'-pyridyl)-methyl]-mercapto}-1H-benzimidazole, and 5-butylaminoformyl-2-{[(3',4'-dimethoxyl-2'-pyridyl)-methyl]-mercapto}-1H-benzimidazole had anti-gastric secretory activities and the last compound was the most potent.

L4 ANSWER 26 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:425825 CAPLUS
DN 131:63462
TI Pharmaceutical preparation in tablet or pellet form for pantoprazole and omeprazole
IN Dietrich, Rango; Ney, Hartmut
PA Byk Gulden Lomberg Chemische Fabrik G.m.b.H., Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19752843	A1	19990701	DE 1997-19752843	19971128
	DE 19752843	C2	20030109		
PRAI	DE 1997-19752843		19971128		

AB Coated tablets or pellets for treatment of excessive gastric acid secretion are provided which comprise a core containing an H+,**K**+-**ATPase** inhibitor (pantoprazole or omeprazole) in an alkaline matrix, and ≥1 coatings of gastric acid-resistant film-forming polymer, of which that in immediate contact with the core is neutralized, e.g. with an alkali metal carbonate or hydroxide, amine, or NH4OH. The coating material is a methacrylic acid/methacrylate ester copolymer, cellulose derivative, and/or poly(vinyl acetate phthalate). If the coating is applied as an aqueous solution or dispersion, no organic solvents need be used in manufacture of the tablets or pellets. Thus, tablet cores were prepared containing Na pantoprazole-1.5H2O 45.1, Na2CO3 10.0, mannitol 42.7, insol. Polyvidone 50.0, Polyvidone K90 4.0, and Ca stearate 3.2 mg. These were coated with a neutralized film containing Eudragit L30D 9.84, tri-Et citrate 0.29, and Na2CO3 0.78 mg/tablet applied as an aqueous solution, and then spray-coated with a dispersion containing Eudragit L30D 13.64 and tri-Et citrate 1.36 mg/tablet.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:221693 CAPLUS
DN 131:67920
TI Proton pump inhibitor: effects of pantoprazole, a novel H+/**K**+-**ATPase** inhibitor, on duodenal ulcerogenic and healing responses in rats: a comparative study with omeprazole and lansoprazole
AU Takeuchi, Koji; Konaka, Akira; Nishijima, Masato; Kato, Shinichi; Yasuhiro, Tetsuya
CS Department of Pharmacology and Experimental Therapeutics, Kyoto Pharmaceutical University, Kyoto, 607-8414, Japan

SO Journal of Gastroenterology and Hepatology (1999), 14(3), 251-257
CODEN: JGHEEO; ISSN: 0815-9319
PB Blackwell Science Asia Pty Ltd.
DT Journal
LA English
AB Pantoprazole, 2-[(2-pyridylmethyl)sulfinyl]benzimidazole, is a new substituted benzimidazole that inhibits the parietal cell H+/**K**+-**ATPase**. In the present study, the anti-secretory and anti-ulcer activities of pantoprazole were compared with those of omeprazole and lansoprazole in rats. Pantoprazole (0.3-3 mg/kg, p.o.) as well as omeprazole (1-10 mg/kg, p.o.) and lansoprazole (1-10 mg/kg, p.o.) dose-dependently decreased both basal acid secretion in pylorus-ligated rats and the stimulated acid secretion induced by mepirizole in acute fistula rats, and the effects of pantoprazole were more potent than those of omeprazole and lansoprazole, the ED50 values for the stimulated acid secretion being 0.8, 2.0 and 1.2 mg/kg, resp. Neither of these drugs had any effect on duodenal HCO3- secretion. These pump inhibitors prevented the development of duodenal lesions in response to mepirizole in a dose-related manner, the ED50 values for pantoprazole, omeprazole and lansoprazole being 0.4, 2.0 and 1.3 mg/kg, resp. Likewise, pantoprazole showed the healing promoting action on chronic duodenal ulcers induced by acetic acid, and this effect was also more potent when compared to omeprazole or lansoprazole. The authors conclude that pantoprazole exhibited both anti-ulcer and healing promoting effects on duodenal ulcers in rats, and the effects may be attributable to its potent anti-secretory action. Other pump inhibitors such as omeprazole and lansoprazole were almost equally effective as pantoprazole, yet this drug was most potent on the basis of ED50 values.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:377829 CAPLUS
DN 129:103723
TI Pharmacokinetics of pantoprazole in patients with end-stage renal failure
AU Kliem, Volker; Bahlmann, Jens; Hartmann, Manfred; Huber, Reinhard; Luhmann, Reinhold; Wurst, Wilhelm
CS Department of Medicine, Division of Nephrology, Medical School Hannover, Hannover, Germany
SO Nephrology, Dialysis, Transplantation (1998), 13(5), 1189-1193
CODEN: NDTREA; ISSN: 0931-0509
PB Oxford University Press
DT Journal
LA English
AB Pantoprazole is a selective inhibitor of the gastric H+/**K**+-**ATPase** with a low potential to interact with the cytochrome P 450 enzyme system. Since pantoprazole is metabolized in the liver to metabolites which are mainly cleared by the renal route, it was the aim of this study to investigate its pharmacokinetics in patients with end-stage renal failure undergoing regular hemodialysis. Eight patients with end-stage renal failure (creatinine clearance < 5 mL/min, age 45-65 yr) on regular hemodialysis (duration of hemodialysis 4-5 h, cuprophan-dialyzer Hemoflow E3, surface 1.3 m2) were given single i.v. doses of 40 mg pantoprazole one day before hemodialysis (A) and on a hemodialysis day immediately before the start of the hemodialysis (B). Concns. of pantoprazole and metabolite M2 were determined in plasma and urine over 24 h and in timed samples of the dialysis fluid by HPLC. The protein binding was determined using equilibrium dialysis. The pharmacokinetic characteristics of pantoprazole AUC, t1/2, CL and Vd area (geometric means) were 2.4 mgxh/l, 0.63 h, 0.227 l/h/kg and 0.206 l/kg on day A (without dialysis) and 2.3 mgxh/l, 0.8 h, 0.237 l/h/kg and 0.273 l/kg on day B (with dialysis), resp.

The protein binding was 96%. Pantoprazole was found in small amts. in the dialysis fluid (maximum 2.1% of the dose) but not in the urine. Pantoprazole was well tolerated. In particular, there were no clin. relevant changes in blood count, electrolytes or liver enzymes. Haemodialysis has no influence on the pharmacokinetic characteristics of pantoprazole. Thus, pantoprazole is not dialyzed to any relevant degree, and therefore no dose-adjustment is required for patients with end-stage renal failure undergoing regular hemodialysis treatment.

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:355396 CAPLUS
DN 129:12284
TI Comparative pharmacokinetic/pharmacodynamic analysis of proton pump inhibitors omeprazole, lansoprazole, and pantoprazole, in humans
AU Katashima, Masataka; Yamamoto, K.; Tokuma, Y.; Hata, T.; Sawada, Y.; Iga, T.
CS Biopharmaceutical Pharmacokinetic Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., Osaka, 532, Japan
SO European Journal of Drug Metabolism and Pharmacokinetics (1998), 23(1), 19-26
CODEN: EJDPD2; ISSN: 0378-7966
PB Medecine et Hygiene
DT Journal
LA English
AB The relationship between plasma concns. and inhibitory effects on gastric acid secretion by proton pump inhibitors (PPIs) omeprazole (OPZ), lansoprazole (LPZ) and pantoprazole (PPZ), was analyzed using a pharmacokinetic/pharmacodynamic (PK/PD) model in humans. The estimated values of apparent reaction rate constant of PPI and H+,**K+-ATPase** (K) were 1.34 ± 0.17 (μM-1.h-1), 0.339 ± 0.002 and 0.134 ± 0.006 for OPZ, LPZ and PPZ, resp. The estimated values of apparent turn-over rate constant of H+,**K+-ATPase** (k) were 0.0252 ± 0.0019 (h-1), 0.0537 ± 0.0006 and 0.0151 ± 0.0002 for OPZ, LPZ and PPZ, resp. The apparent dissociation consts. of the H+,**K+-ATPase**-PPI complex (k/K.fp) corrected with plasma free fraction (fp) were about 1 nM for OPZ and LPZ and 2.3 nM for PPZ. Therefore, the potency of the inhibitory effect of PPZ on acid secretion may be slightly weaker than that of OPZ or LPZ. The apparent half lives (ln2/k) of the inhibitory effect on acid secretion were 12.9 h for LPZ, <27.5 h for OPZ, and <45.9 h for PPZ, the recovery rate of the inhibitory effect of PPZ on acid secretion was slowest among these PPIs. In conclusion, the relationship between plasma concns. and inhibitory effects of PPIs on gastric acid secretion could be analyzed by the PK/PD model.

L4 ANSWER 30 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:76454 CAPLUS
DN 128:97546
TI Differences in pH-dependent activation rates of substituted benzimidazoles and biological in vitro correlates
AU Kromer, Wolfgang; Krueger, U.; Huber, R.; Hartmann, M.; Steinijans, V. W.
CS Dep. Pharmacology, Byk Gulden, Konstanz, D-78467, Germany
SO Pharmacology (1998), 56(2), 57-70
CODEN: PHMGBN; ISSN: 0031-7012
PB S. Karger AG
DT Journal
LA English
AB Gastric proton pump inhibitors (PPIs) are substituted benzimidazole pro-drugs that require an acid-induced activation. Its rate depends on the reactivity of the mol. relative to the environmental pH and dets. the drug's tissue selectivity. Factors affecting the exposure of moderately

acidic tissues to the activated PPI are the area under the serum concentration-time curve (AUC), serum protein binding, the partition coefficient logP, and the serum elimination half-life relative to the chemical activation half-life at a critical tissue pH of about 5. These parameters have therefore been determined in a comparative fashion in the present study. The data shows that pantoprazole is less likely to undergo unwanted activation at moderately acidic targets as opposed to the parietal cell, compared to omeprazole. Actually, although 40 mg pantoprazole (steady state) gave a slightly higher serum AUC of the total parent compound than 40 mg omeprazole (10.5 vs. 7.1 μmol + h + 1-1), a higher serum protein binding of pantoprazole vs. omeprazole (98 vs. 96%) reversed the AUC values for the free drug in favor of a lower value for pantoprazole (0.19 vs. 0.28 μmol + h + 1-1). It is the free parent compound that equilibrates across cell membranes to be activated in acidic tissue compartments. At pH 5.1, the activation half-life of pantoprazole was 4.7 vs. 1.4 h for omeprazole, the latter being in the order of the common serum elimination half-life determined in an intraindividual comparison (1.24 vs. 1.25 h). Thus, pantoprazole is eliminated faster from blood than it is activated at a pH of about 5, while omeprazole is as quickly activated at this pH as it is eliminated from blood. Biol. in vitro expts. confirmed that pantoprazole displays a lower liability to interfere with unwanted biol. targets. This has been demonstrated in vitro for inhibition of both renal Na+/ **K+-ATPase**, lysosomal acidification, and the production of reactive oxygen species by neutrophils.

L4 ANSWER 31 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:35221 CAPLUS
DN 128:97543
TI Effects of pantoprazole, a novel H+/**K+ ATPase** inhibitor, on gastroduodenal secretion and duodenal ulcerogenic and healing responses in rat. A comparative study with omeprazole
AU Yasuhiro, Tetsuya; Konaka, Akira; Nishijima, Masato; Kato, Shinichi; Takeuchi, Koji
CS Dep. Pharm. Exp. Therapeutics, Kyoto Pharm. Univ., Kyoto, 607, Japan
SO Therapeutic Research (1997), 18(11), 3629-3638
CODEN: THREEL; ISSN: 0289-8020
PB Raifu Saiensu Shuppan K.K.
DT Journal
LA Japanese
AB Pantoprazole (Pan), a novel H+/**K+ATPase** inhibitor, has been synthesized by optimizing the structure of substituted benzimidazoles in order to further improve selectivity for the secreting parietal cell. In this study, we examined the effects of Pan on gastric acid secretion, duodenal HCO3- secretion, and duodenal ulcerogenic and healing responses in rats, in comparison with omeprazole (Ome). Both Pan and Ome dose-dependently inhibited acid secretion in pylorus-ligated rats; the effect of Pan was 3 times potent than Ome. Either agent also inhibited gastric acid secretory response induced by mepirizole; ED50 was 0.8 mg/kg and 2.0 mg/kg, resp., while duodenal HCO3- secretion was not affected by either of these agents. On the other hand, mepirizole caused severe damage in the proximal duodenum within 24 h, and this ulcerogenic response was dose-dependently inhibited by either Pan or Ome; ED50 was 0.4 mg/kg and 2.0 mg/kg, resp. These agents dose-dependently promoted the healing of acetic acid-induced duodenal ulcers, when administered at 1.apprx.10 mg/kg p.o. once daily for 7 days starting 3 day after the acid treatment, the healing rate at 10 mg/kg was 77.9% for Pan and 64.6% for Ome. These results suggest that (1) Pan exhibited a potent antisecretory action on basal and mepirizole-stimulated acid secretion, the effect being 2.5.apprx.3 times potent than Ome, (2) Pan showed the mucosal protective action on acute duodenal lesions as well as the healing promoting effect on chronic duodenal ulcers, these effects also being more potent than Ome,

and (3) the mechanism of mucosal protection by Pan, but not Ome, may involve other actions in addition to acid inhibition, because Ed50 for the mucosal protection was 2 times less than that for antisecretory action.

L4 ANSWER 32 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:14852 CAPLUS
DN 128:136346
TI One-year prophylactic efficacy and safety of pantoprazole in controlling gastro-esophageal reflux symptoms in patients with healed reflux esophagitis
AU Mossner, J.; Koop, H.; Porst, H.; Wubbolding, H.; Schneider, A.; Maier, C.
CS Universitatsklinikum Leipzig, Leipzig, Germany
SO Alimentary Pharmacology and Therapeutics (1997), 11(6), 1087-1092
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB Pantoprazole is a benzimidazole derivative which selectively inhibits the proton pump H+, **K+-ATPase** necessary for the final step in gastric acid secretion. To investigate the tolerability and the prophylactic effect of pantoprazole 40 mg once daily on relapse in patients whose reflux esophagitis had been healed. The safety of pantoprazole 40 mg once daily was assessed in an open 1-yr trial on 222 patients whose reflux esophagitis had been healed with omeprazole or pantoprazole. Relapse was defined as endoscopically-confirmed reflux esophagitis (at least Grade I), with endoscopies being performed for patients experiencing 3 consecutive days of disease-specific symptoms. Kaplan-Meier survival anal. at 6 and 12 mo gave estimated treatment failure rates of 2% and 6% from confirmed relapses (per-protocol), and of 9% and 30% for a worst-case group (all withdrawals counted as failures). The only population shift in laboratory variables was a doubling of the median serum gastrin level over the first 6 mo; thereafter it stabilized. Fifty-four (24%) patients experienced adverse events; 15 of these withdrew. Serious adverse events were reported for 12 patients. Pantoprazole appears to be highly effective and to have a good safety profile for long-term prophylaxis of reflux esophagitis.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:455074 CAPLUS
DN 127:156080
TI Pantoprazole: a new and more specific proton pump inhibitor
AU Garner, Andrew; Fadlallah, Hassan
CS UK
SO Expert Opinion on Investigational Drugs (1997), 6(7), 885-893
CODEN: EOIDER; ISSN: 0967-8298
PB Ashley Publications
DT Journal; General Review
LA English
AB A review with 55 refs. Pantoprazole is the third proton pump inhibitor (PPI) to be launched for the treatment of acid-peptic diseases. Like other drugs in this class, pantoprazole causes long-lasting inhibition of acid secretion by inactivating the parietal cell H+/**K+-ATPase**. Compared with H2 antagonists, pantoprazole results in faster pain relief, more rapid ulcer healing, healing of resistant ulcers and far greater efficacy in esophageal reflux disease. The three PPIs currently available display almost identical efficacy in the treatment of acid-peptic diseases and when included as part of Helicobacter pylori eradication regimes. However, pantoprazole shows improvements in selectivity and pharmacokinetic properties compared with omeprazole and

lansoprazole. The bioavailability of pantoprazole is considerably higher than omeprazole, remains constant upon repeated dosing, and is unaffected by food. Significantly, pantoprazole does not influence hepatic cytochrome P 450 activity and does not therefore interact with co-administered drugs. This is in contrast to omeprazole, which inhibits P 450, and lansoprazole, which appears to weakly induce multiple metabolic pathways. Although pantoprazole is entering an antisecretory market dominated by omeprazole and ranitidine, it has a number of potential advantages. In this respect it is worth recalling that enhanced specificity and the absence of drug interactions were decisive factors in determining market share in the H2 antagonist era. Pantoprazole may therefore achieve significant market penetration, particularly at the expense of lansoprazole and the H2 blockers.

L4 ANSWER 34 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:332242 CAPLUS
DN 127:75438
TI An updated review of pantoprazole drug interactions in man.
AU Steinijans, V. W.; Huber, R.; Hartmann, M.; Zech, K.; Bliesath, H.; Wurst, W.; Radtke, H. W.
CS Byk Gulden Pharmazeutika, Konstanz, D-78467, Germany
SO Verdauungskrankheiten (1997), 15(2), 77-96
CODEN: VERDEJ; ISSN: 0174-738X
PB Dustri-Verlag Dr. Karl Feistle
DT Journal; General Review
LA German
AB This review with 124 refs. summarizes the results of pharmacokinetic and pharmacodynamic drug interaction studies in man with pantoprazole, a new, selective proton pump inhibitor (PPI). PPIs may alter the adsorption of drugs by increasing the intragastric pH. With the increasing use of PPIs, their interaction potential gains therapeutic importance. The high selectivity of pantoprazole to the gastric H+/**K+-ATPase** characterizes this new PPI. In the drug interaction studies so far, substrates for all relevant cytochrome P 450 families involved in the metabolism of drugs in man were investigated. Pantoprazole did not affect the pharmacokinetics or pharmacodynamics of antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, EtOH, glibenclamide, a hormonal contraceptive (combination of levonorgestrel and ethinylestradiol), metoprolol, nifedipine, phenprocoumon, phenytoin, theophylline, and warfarin in man. Pantoprazole also neither induced the metabolism of antipyrine or caffeine, nor increased urinary excretion of the induction markers D-glucaric acid and 6β-hydroxycortisol. Vice versa, the investigated drugs had no relevant influence on the pharmacokinetics of pantoprazole.

L4 ANSWER 35 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:212325 CAPLUS
DN 126:271731
TI A HPLC method to determine pantoprazole plasma concentration
AU Wang, Dongkai; Fang, Fang; Miao, Suoning; Ren, Jixia; Qi, Jing; Xu, Yajie; Guo, Yali
CS Institute of Materia Medica, Shenyang Pharmaceutical University, Shenyang, 110015, Peop. Rep. China
SO Shenyang Yaoke Daxue Xuebao (1996), 13(4), 246-250
CODEN: SYDXFF; ISSN: 1006-2858
PB Shenyang Yaoke Daxue Xuebao Bianjibu
DT Journal
LA Chinese
AB A reverse phase HPLC method was developed to determine the plasma concentration of the new H+/**K+ ATPase** inhibitor--pantoprazole. MeOH/H2O/TEA (61:31:1) was used as the mobile phase. The monitoring

wavelength was 290 nm. The specificity, accuracy, precision, and sensitivity were tested in this method. The average recovery was 91.36%. The linearity range was given.

L4 ANSWER 36 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:535864 CAPLUS
DN 125:184852
TI Lack of pharmacokinetic interaction of pantoprazole with diazepam in man
AU Gugler, R.; Hartmann, M.; Rudi, J.; Brod, I.; Huber, R.; Steinijans, V. W.; Bliesath, H.; Wurst, W.; Klotz, U.
CS Klinikum Karlsruhe, Karlsruhe, 76133, Germany
SO British Journal of Clinical Pharmacology (1996), 42(2), 249-252
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell
DT Journal
LA English
AB Pantoprazole, a substituted benzimidazole, is a potent and well tolerated inhibitor of the gastric H+,K+-**ATPase** with a low potential to inhibit cytochrome P 450. In this randomized, placebo-controlled two-period crossover study, 12 healthy volunteers received placebo (reference) and 240 mg of pantoprazole (test) i.v. within 2 min once daily for 7 days each. On day 4 of either period, a 1 min bolus of diazepam (0.1 mg kg-1 body weight) was addnl. injected. Pantoprazole was well tolerated and did not cause clin. relevant changes in heart rate, blood pressure, ECG and routine clin. laboratory parameters. There was no effect on diazepam clearance (0.021 1 h-1 kg-1 for test and reference) and elimination half-life (36.8 h for test, 40.4 h for reference). Diazepam metabolism to desmethyldiazepam was not affected by pantoprazole. In conclusion, pantoprazole and diazepam may be administered concomitantly without dose adjustment even when high doses of pantoprazole are required.

L4 ANSWER 37 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:426431 CAPLUS
DN 125:104007
TI Lack of pantoprazole drug interactions in man: An updated review
AU Steinijans, V. W.; Huber, R.; Hartmann, M.; Zech, K.; Bliesath, H.; Wurst, W.; Radtke, H. W.
CS Byk Gulden Pharmaceuticals, Konstanz, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1996), 34(Suppl. 1, Pantoprazole: Pharmacokinetics and Drug Interactions in Man), 531-550
CODEN: ICTHEK; ISSN: 0946-1965
PB Dustri-Verlag Dr. Karl Feistle
DT Journal; General Review
LA English
AB This review, with >100 refs., summarizes the results of pharmacokinetic and pharmacodynamic drug interaction studies in man with pantoprazole, a new, selective proton pump inhibitor. Various mechanisms have to be considered as causes for potential drug-drug interactions. Proton pump inhibitors (PPIs) in general may alter the absorption of drugs by increasing the intragastric pH. Due to the presence of an imidazole ring, the PPIs of the class of substituted benzimidazole sulfoxides may interfere with the metabolism of other drugs by altering the activity of drug metabolizing enzymes of the cytochrome P 450 system, via either induction or inhibition. With the increasing use of PPIs, their interaction potential gains therapeutic importance as was the case with the first and second generation of H2-blockers (cimetidine and ranitidine, resp.). The enhanced selectivity of pantoprazole to the gastric H+/K+-**ATPase** characterizes the new PPI generation. In contrast to omeprazole, pantoprazole has a low potential to interact with the cytochrome P 450 system in man. In the drug interaction studies conducted

so far, substrates for all relevant cytochrome P 450 families involved in the metabolism of drugs in man were investigated. Pantoprazole did not affect the pharmacokinetics or pharmacodynamics of antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, a hormonal contraceptive (combination of levonorgestrel and ethinylestradiol), metoprolol, nifedipine, phenprocoumon, phenytoin, theophylline and warfarin in man. Pantoprazole also neither induced the metabolism of antipyrine or caffeine, nor increased urinary excretion of the induction markers D-glucaric acid and 6β-hydroxycortisol. Vice versa, the investigated drugs had no relevant influence on the pharmacokinetics of pantoprazole.

L4 ANSWER 38 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:423554 CAPLUS
DN 125:103979
TI Lack of pantoprazole drug interactions in man: An updated review
AU Steinijans, V. W.; Huber, R.; Hartmann, M.; Zech, K.; Bliesath, H.; Wurst, W.; Radtke, H. W.
CS Byk Gulden Pharmaceuticals, Konstanz, D-78467, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1996), 34(6), 243-262
CODEN: ICTHEK; ISSN: 0946-1965
PB Dustri-Verlag Dr. Karl Feistle
DT Journal; General Review
LA English
AB This review, with >100 refs., summarizes the results of pharmacokinetic and pharmacodynamic drug interaction studies in man with pantoprazole, a new, selective proton pump inhibitor. Various mechanisms have to be considered as causes for potential drug-drug interactions. Proton pump inhibitors (PPIs) in general may alter the absorption of drugs by increasing the intragastric pH. Due to the presence of an imidazole ring, the PPIs of the class of substituted benzimidazole sulfoxides may interfere with the metabolism of other drugs by altering the activity of drug metabolizing enzymes of the cytochrome P 450 system, via either induction or inhibition. With the increasing use of PPIs, their interaction potential gains therapeutic importance as was the case with the first and second generation of H2-blockers (cimetidine and ranitidine, resp.). The enhanced selectivity of pantoprazole to the gastric H+/K+-**ATPase** characterizes the new PPI generation. In contrast to omeprazole, pantoprazole has a low potential to interact with the cytochrome P 450 system in man. In the drug interaction studies conducted so far, substrates for all relevant cytochrome P 450 families involved in the metabolism of drugs in man were investigated. Pantoprazole did not affect the pharmacokinetics or pharmacodynamics of antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, a hormonal contraceptive (combination of levonorgestrel and ethinylestradiol), metoprolol, nifedipine, phenprocoumon, phenytoin, theophylline and warfarin in man. Pantoprazole also neither induced the metabolism of antipyrine or caffeine, nor increased urinary excretion of the induction markers D-glucaric acid and 6β-hydroxycortisol. Vice versa, the investigated drugs had no relevant influence on the pharmacokinetics of pantoprazole.

L4 ANSWER 39 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:398394 CAPLUS
DN 125:75967
TI Efficacy and tolerability of pantoprazole 40 mg versus 80 mg in patients with reflux esophagitis
AU Van Rensburg, C. J.; Honiball, P. J.; Grundling, H. De K.; Van Zyl, J. H.; Spies, S. K.; Eloff, F. P.; Simjee, A. E.; Segal, I.; Botha, J. F.; et al.
CS Departments Medicine and Gastroenterology, Universities Stellenbosch, S. Afr.

SO Alimentary Pharmacology and Therapeutics (1996), 10(3), 397-401
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell
DT Journal
LA English
AB Pantoprazole is a substituted benzimidazole which is a potent inhibitor of gastric acid secretion by its action upon H+,**K+-ATPase**. Pantoprazole 40 mg and 80 mg were compared in a randomized double-blind study in 192 out-patients with stage II or III (Savary-Miller classification) reflux esophagitis. Patients received either pantoprazole 40 mg or pantoprazole 80 mg, once daily before breakfast for 4 wk. Treatment was extended for a further 4 wk if the esophagitis had not healed. After 4 wk complete healing of the reflux esophagitis was seen in 78% of protocol-correct patients given pantoprazole 40 mg daily, and in 72% in the 80 mg group. The cumulative healing rates after 8 wk were 95 and 94%, resp. (Cochran-Mantel-Haenszel), and time until healing of esophagitis comparable in both groups. Differences between doses were also not significant in an intention-to-treat anal. Both dosing schedules were well tolerated and the patients experienced remarkable symptom relief. No adverse event or changes in laboratory values of clin. significance could definitely be ascribed to the trial medication. The 40 mg pantoprazole dosage is comparable to 80 mg in reflux esophagitis, both in efficacy and tolerability.

L4 ANSWER 40 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:292515 CAPLUS
DN 125:245
TI Lack of pharmacokinetic interaction between pantoprazole and diclofenac
AU Bliesath, H.; Huber, R.; Steinuans, V. W.; Koch, H. J.; Wurst, W.; Mascher, H.
CS Research Division Byk Gulden Pharmaceuticals, Konstanz, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1996), 34(4), 152-156
CODEN: ICTHEK; ISSN: 0946-1965
PB Dustri-Verlag Dr. Karl Feistle
DT Journal
LA English
AB The new H+/**K+ ATPase** inhibitor pantoprazole is extensively metabolized by the liver. As substituted benzimidazoles may potentially interact with the cytochrome P 450 system, the influence of pantoprazole on the pharmacokinetics of the NSAID diclofenac was investigated. Diclofenac is widely used in the treatment of rheumatic diseases and is mainly metabolized in the liver by CYP2C9. Twenty-four healthy volunteers (13 male/11 female) completed a randomized crossover study. As test they received orally 40 mg pantoprazole and concomitantly 100 mg diclofenac. As resp. refs. 100 mg diclofenac or 40 mg pantoprazole were given alone. Diclofenac and pantoprazole serum concns. were measured. Lack of pharmacokinetic interaction was handled as an equivalence problem. The 90% confidence intervals (CI) of the ratios of the primary characteristic AUC and the secondary characteristic Cmax of diclofenac were entirely within the equivalence range of 0.8 - 1.25. Hence, no influence of pantoprazole on the pharmacokinetics of diclofenac was concluded, either by competition with the CYP2C9 or by the reduction of gastric acid secretion. Vice versa, diclofenac did not affect the pharmacokinetics of pantoprazole. All treatments were safe and well tolerated. No dose adjustment is required during concomitant treatment with diclofenac and pantoprazole.

L4 ANSWER 41 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:177722 CAPLUS
DN 124:277886
TI Pantoprazole does not interact with nifedipine in man under steady-state

conditions
AU Bliesath, H.; Huber, R.; Steinijans, V. W.; Koch, H. J.; Kunz, K.; Wurst, W.
CS Research Division, Byk Gulden Pharmaceuticals, Konstanz, D-78403, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1996), 34(2), 51-5
CODEN: ICTHEK; ISSN: 0946-1965
PB Dustri-Verlag Dr. Karl Feistle
DT Journal
LA English
AB The new H+/**K+-ATPase** inhibitor pantoprazole is extensively metabolized by the liver. As substituted benzimidazoles can interact with the cytochrome P 450 system, the influence of pantoprazole on the steady-state pharmacokinetics of the calcium antagonist nifedipine was investigated. Nifedipine is widely used in the treatment of cardiovascular diseases and is mainly metabolized in the liver by CYP3A4. Addnl., possible influence of gastric pH on the absorption of nifedipine is discussed. Twenty-four healthy volunteers (13 m/11 f) completed a randomized crossover study. As test they received orally 40 mg pantoprazole s.i.d. for 10 days and concomitantly 20 mg nifedipine sustained-release (SR) b.i.d. from day 6 to 10. During the reference period 20 mg nifedipine SR were dosed b.i.d. for 5 days. Nifedipine and pantoprazole serum concns. were measured over one dosing interval on the last day of each period. Lack of pharmacokinetic interaction was handled as an equivalence problem. The 90%-confidence intervals (CI) of the ratios of the primary characteristics AUC and Cmax of nifedipine were entirely within the equivalence range of 0.8-1.25. Hence no influence of pantoprazole on the pharmacokinetics of nifedipine was concluded, either by competition with the CYP3A4 or by the reduction of gastric acid secretion. As secondary criterion nifedipine had no relevant influence on the pantoprazole pharmacokinetic characteristics. All treatments were safe and well tolerated. No dose adjustment is required during concomitant treatment with nifedipine and pantoprazole.

L4 ANSWER 42 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:171958 CAPLUS
DN 124:212082
TI Multiple unit pharmaceutical preparations containing proton pump inhibitor
IN Bergstrand, Pontus John Arvid; Loevgren, Kurt Ingmar
PA Astra Aktiebolag, Swed.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9601624	A1	19960125	WO 1995-SE678	19950607
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2170644	AA	19960125	CA 1995-2170644	19950607
	CA 2170995	AA	19960126	CA 1995-2170995	19950607
	AU 9529938	A1	19960209	AU 1995-29938	19950607
	AU 695971	B2	19980827		
	EP 723437	A1	19960731	EP 1995-926055	19950607
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CN 1134667	A	19961030	CN 1995-190816	19950607

	CN 1134668	A	19961030	CN 1995-190819	19950607
	JP 09502740	T2	19970318	JP 1995-504249	19950607
	HU 75934	A2	19970528	HU 1996-574	19950607
	BR 9506028	A	19971014	BR 1995-6028	19950607
	EE 3292	B1	20001016	EE 1996-32	19950607
	PL 180598	B1	20010330	PL 1995-313388	19950607
	RU 2166935	C2	20010520	RU 1996-107040	19950607
	SK 283841	B6	20040302	SK 1996-300	19950607
	TW 421599	B	20010211	TW 1995-84106116	19950615
	US 5753265	A	19980519	US 1995-464774	19950622
	ZA 9505546	A	19960108	ZA 1995-5546	19950704
	ZA 9505547	A	19960108	ZA 1995-5547	19950704
	IL 114447	A1	20020912	IL 1995-114447	19950704
	FI 9601058	A	19960307	FI 1996-1058	19960307
	FI 9601059	A	19960307	FI 1996-1059	19960307
	NO 9600948	A	19960307	NO 1996-948	19960307
PRAI	SE 1994-2431	A	19940708		
	WO 1995-SE678	W	19950607		

OS MARPAT 124:212082

AB A new pharmaceutical multiple unit tabletted dosage form containing an acid labile H+**K**+-**ATPase** inhibitor or an alkaline salt thereof or one of its single enantiomers or an alkaline salt thereof is claimed. Tablet core containing lansoprazole 400, sugar sphere seeds 400, HPMC 82, Na lauryl sulfate 3, and water 1600 were coated with a separating layer in a fluid bed apparatus containing talc and Mg stearate and HPMC. An enteric coating solution cong. methacrylic acid copolymer and polysorbate and glycerides was sprayed onto the pellets covered with separating layer in a fluid bed apparatus Enteric coating layer pellets 82 and microcryst. cellulose 191 g were mixed and compressed into tablets.

L4 ANSWER 43 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1996:155490 CAPLUS

DN 124:202255

TI Preparation of sulfur-containing heterocyclic (H+/**K**+) **ATPase** inhibitors as antiviral agents

IN Moormann, Alan E.; Becker, Daniel P.; Flynn, Daniel L.; Li, Hui; Villamil, Clara I.

PA G. D. Searle and Co., USA

SO PCT Int. Appl., 212 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9529897	A1	19951109	WO 1995-US5021	19950501
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9523950	A1	19951129	AU 1995-23950	19950501
	US 5945425	A	19990831	US 1996-737251	19961024
	US 2001047038	A1	20011129	US 2001-885221	20010620
PRAI	US 1994-235619	A2	19940429		
	WO 1995-US5021	W	19950501		
	US 1996-659098	B1	19960604		
	US 1999-377888	B1	19990819		
	US 2000-605560	B1	20000627		

OS MARPAT 124:202255
AB The title compds., which are (H+/**K**+) **ATPase** inhibitors, useful for the treatment of viral infections, are prepared and formulations containing them are claimed. Thus, 2-[(1H-benzimidazol-2-yl)sulfinylmethyl]-N,N-dimethylbenzenamine, m.p. 107-109°, was prepared and demonstrated a (H+/**K**+) **ATPase** IC50 of 0.7 μM.

L4 ANSWER 44 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:138417 CAPLUS
DN 124:250427
TI Pantoprazole and omeprazole in the treatment of reflux esophagitis: A European multicenter study
AU Corinaldesi, R.; Valentini, M.; Belaiche, J.; Colin, R.; Geldof, H.; Maier, C.
CS Ospedale S. Orsola, Bologna, 40138, Italy
SO Alimentary Pharmacology and Therapeutics (1995), 9(6), 667-71
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell
DT Journal
LA English
AB Pantoprazole is a new substituted benzimidazole which inhibits gastric H+, **K+-ATPase**. In this double-blind, multicenter study, pantoprazole 40 mg once daily was compared with omeprazole 20 mg once daily in the treatment of grade II and III (Savary-Miller) reflux esophagitis. Endoscopy was repeated after 4 wk of treatment, and also after 8 wk in patients unhealed at 4 wk. The primary efficacy variable was ulcer healing; after 4 wk, 81/103 (78.6%) patients in the pantoprazole group and 83/105 (79.0%) patients in the omeprazole group had healed completely. After 8 wk, the cumulative healing rates were 94.2% and 91.4% in the pantoprazole and omeprazole groups, resp. ($P > 0.05$ at 4 wk and 8 wk). Both groups experienced rapid relief of the key symptoms: heartburn, acid regurgitation and pain on swallowing. The time course of relief of the individual symptoms was similar in both groups after 2 and 4 wk ($P > 0.05$). Both treatments were well tolerated, with only three patients withdrawing owing to adverse events. Conclusion: Pantoprazole has been shown to be as effective as omeprazole in the treatment of reflux esophagitis.

L4 ANSWER 45 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:671093 CAPLUS
DN 121:271093
TI Lack of pantoprazole drug interactions in man
AU Steinijans, V. W.; Huber, R.; Hartmann, M.; Zech, K.; Bliesath, H.; Wurst, W.; Radtke, H. W.
CS Byk Gulden Pharmaceuticals, Konstanz, D-78403, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1994), 32(8), 385-99
CODEN: ICTHEK; ISSN: 0946-1965
DT Journal; General Review
LA English
AB A review with 74 refs. This review summarizes the results of pharmacokinetic and pharmacodynamic drug interaction studies in man with pantoprazole, a new, selective proton pump inhibitor. Different mechanisms have to be considered as causes for potential drug-drug interactions. Proton pump inhibitors (PPIs) in general may alter the absorption of drugs by increasing the intragastric pH. Due to the presence of an imidazole ring, the PPIs of the class of substituted benzimidazole sulfoxides may interfere with the metabolism of other drugs by altering the activity of drug metabolizing enzymes of the cytochrome P 450 system, via either induction or inhibition. With the increasing use of PPIs, their interaction potential gains therapeutic importance as was the

case with the first and second generation of H2-blockers (cimetidine and ranitidine, resp.). The enhanced selectivity of pantoprazole to the gastric H+/**K**+-**ATPase** characterizes the new PPI generation. In comparison to omeprazole and lansoprazole, pantoprazole showed a much lower affinity to cytochrome P 450 in vitro and a markedly lower potency in the in vivo rat model for interaction with diazepam. In contrast to omeprazole, pantoprazole does not interact with the cytochrome P 450 system in man. In the drug interaction studies conducted so far, pantoprazole did not affect the pharmacokinetics or pharmacodynamics of antipyrine, diazepam, digoxin, a hormonal contraceptive, nifedipine, phenytoin, theophylline and warfarin in man. Also pantoprazole neither induced the drug metabolism of antipyrine nor increased urinary excretion of the induction markers D-glucaric acid and 6β-hydroxycortisol. Vice versa, the investigated drugs had no relevant influence on the pharmaco-kinetics of pantoprazole.

L4 ANSWER 46 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:524495 CAPLUS
DN 121:124495
TI Dose linearity of the pharmacokinetics of the new H+/**K**+-**ATPase** inhibitor pantoprazole after single intravenous administration
AU Bliesath, H.; Huber, R.; Hartmann, M.; Luehmann, R.; Wurst, W.
CS Res. Div., Byk Gulden Pharm., Konstanz, D-78403, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1994), 32(1), 44-50
CODEN: ICTHEK; ISSN: 0946-1965
DT Journal
LA English
AB Pantoprazole is a specific inhibitor of the H+/+-ATPase of the gastric parietal cell. The dose-dependency of a range of pantoprazole pharmacokinetic characteristics was studied. Twelve healthy male subjects were given 10, 20, 40 and 80 mg pantoprazole i.v. according to a randomized, single blind, 4-period change-over scheme. The area under the concentration vs time curve (AUC) and the maximum serum concentration (Cmax) showed a linear increase in line with the dose. Apparent volume of distribution (Vd area), clearance (Cl) and terminal half-life (t1/2) were independent of the dose. The dose-independent elimination of pantoprazole was attributed to the lack of interaction of the drug with cytochrome P 450. In clin. practice, a good predictable response, as well as a low potential for interaction with other drugs might be expected.

L4 ANSWER 47 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:499016 CAPLUS
DN 121:99016
TI Pantoprazole lacks interaction with antipyrine in man, either by inhibition or induction
AU De Mey, C.; Meineke, I.; Steinijans, V. W.; Huber, R.; Hartmann, M.; Bliesath, H.; Wurst, W.
CS Cent. Cardiovasc. Pharmacol., Mainz, D-55116, Germany
SO International Journal of Clinical Pharmacology and Therapeutics (1994), 32(2), 98-106
CODEN: ICTHEK; ISSN: 0946-1965
DT Journal
LA English
AB Substituted benzimidazole inhibitors of the gastric H+/**K**+-**ATPase** may interact with the cytochrome P 450 enzyme system and alter the pharmacokinetics of coadministered drugs, as known for omeprazole. The primary aim of the present studies was to determine whether pantoprazole, a new, selective proton pump inhibitor, modifies the plasma concns. of orally-administered antipyrine, a commonly used marker for

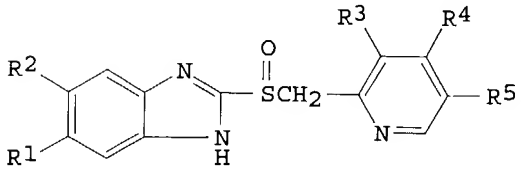
mixed hepatic oxidase enzyme activity. In the acute study, 12 healthy male volunteers were given (a) a single 30 mg i.v. doses of pantoprazole, (b) a single 5 mg/kg oral dose of antipyrine, or (c) coadministered pantoprazole and antipyrine according to a randomized three-period change-over design. In the chronic study, another 12 volunteers received 40 mg once-daily oral doses of pantoprazole on day 3 and on days 5-12, and a single oral 5 mg/kg dose of antipyrine on days 1, 12 and 14. Antipyrine plasma concns. were measured without pantoprazole (day 1), on the last day of chronic dosing with pantoprazole (day 12) and 48 h after the last dose of pantoprazole (day 14) to differentiate between inhibition and induction, resp. Both drugs were well tolerated and no adverse events or clin. relevant alterations in vital signs or laboratory parameters were observed during treatment. The point ests. of the resp. AUC- and Cmax-ratios for antipyrine with and without pantoprazole were 0.99 and 0.98 in the acute study, and 1.01 and 0.93 on day 12, and 1.04 and 0.99 on day 14 of the chronic study. The corresponding 90%-confidence intervals were all within the equivalence range of 0.8-1.25 so that lack of interaction either by inhibition or induction can be concluded.

L4 ANSWER 48 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:472806 CAPLUS
DN 121:72806
TI Continuing development of acid pump inhibitors: Site of action of pantoprazole
AU Shin, J. M.; Besancon, M.; Prinz, C.; Simon, A.; Sachs, G.
CS Dep. Physiol. and Med., UCLA and Veterans Adm. Med. Cent., Los Angeles, CA, 90073, USA
SO Alimentary Pharmacology and Therapeutics (1994), 8(SUPPL. 1, MANAGEMENT OF ACID-RELATED DISEASES: FOCUS ON PANTOPRAZOLE), 11-23
CODEN: APTHEN; ISSN: 0269-2813
DT Journal; General Review
LA English
AB A review with 45 refs. Both receptor antagonists and acid pump inhibitors are clin. useful suppressants of acid secretion. The latter class of drugs, the substituted benzimidazoles, inhibit acid secretion more effectively and, therefore, provide superior symptom relief and healing in all acid-related diseases. The H2-receptor antagonists competitively block the action of histamine on the H2-receptors of parietal cells. This histamine is released from enterochromaffin-like cells (ECL cells) due to gastrin, acetylcholine or epinephrine stimulation. In addition, parietal cells have M3-receptors which can function independently of H2-receptors. Hence, there is no single common pathway for parietal cell stimulation. Stimulation of acid secretion by parietal cells requires activation of the acid pump, the gastric H+,**K+-ATPase**. The target site for the benzimidazoles is the activated gastric H+,**K+-ATPase**, and, in particular, the cysteines of the pump that are exposed to the acid space of the secretory canaliculus of the parietal cells. Pantoprazole in its protonated form selectively reacts with cysteines present in both the fifth and sixth membrane segments of the ATPase, explaining its mechanism of inhibiting proton transport by this enzyme.

L4 ANSWER 49 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:466340 CAPLUS
DN 119:66340
TI The site of action of pantoprazole in the gastric H+/**K+-ATPase**
AU Shin, Jai Moo; Besancon, Marie; Simon, Alexander; Sachs, George
CS Wadsworth VAMC and UCLA, Los Angeles, CA, USA
SO Biochimica et Biophysica Acta (1993), 1148(2), 223-33
CODEN: BBACAQ; ISSN: 0006-3002

DT Journal
LA English
AB Pantoprazole (I) is a pyridinyl-2-methylenesulfinyl-2-benzimidazole derivative This compound inhibits the vesicular gastric (H+,**K**+)-**ATPase** (cytoplasmic side out) under acid transporting conditions by accumulating in the acid space generated by the pump. I is then converted in an acid-catalyzed reaction to a cationic sulfenamide and reacts with cysteines available in or from the acidic extracytoplasmic space. I bound to the hog gastric (H+,**K**+)-**ATPase** with a stoichiometry of 3 nmol/mg protein, resulting in 94% inhibition of ATPase activity. Tryptic cleavage of the intact vesicles which had been reacted with [14C]I at a 1:4 trypsin-to-protein ratio removed most of the cytoplasmic domain leaving the pairs of membrane-spanning segments and their connecting extracytoplasmic loops intact. The peptides remaining in the membrane were dissolved in SDS and the available cysteine residues were labeled with fluorescein 5-maleimide. The peptides were separated on Tricine gradient gels, transferred to polyvinyl difluoride (PVDF) membranes, and identified by fluorescence and radioactivity. From N-terminal sequence, fluorescence, and mol. weight anal., it was concluded that I was able to label both Cys-813 and Cys-822. These cysteines were predicted to be located in the extracytoplasmic loop connecting membrane segments 5 and 6 and in membrane segment 6. The major cytoplasmic tryptic cleavage site at this location moved from position 776 in the unmodified enzyme to positions 784 and 792 following I labeling, showing that the configuration of this region changed with I labeling. A similar result was obtained by reduction of the enzyme with dithiothreitol. Covalent binding of the cationic sulfenamide to this region of the enzyme was able to block the conformation necessary for phosphorylation of the enzyme by ATP, accounting for its inhibitory effect on acid secretion.

L4 ANSWER 50 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:160543 CAPLUS
DN 118:160543
TI Quantum-chemical study of proton pump inhibiting activity of substituted 2-sulfinylbenzimidazoles
AU Jang, Yun Hee; Kim, Hojing
CS Dep. Chem., Seoul Natl. Univ., Seoul, 151-742, S. Korea
SO Korean Journal of Medicinal Chemistry (1992), 2(2), 107-12
CODEN: KJMCE7; ISSN: 1225-0058
DT Journal
LA English
GI



I

AB The relationship between the (H+,**K**+)-**ATPase** inhibitory activity and the electronic structure is evaluated for substituted 2-sulfinylbenzimidazoles (I; R1 = H, OMe, Fe, OCF2O; R2 = OCF2H, OCF2CF3, OCH2CF3, OCH2CF2H, OCF2O, H; R3 = R5 = H, Me, OMe; R4 = OMe, OCH2CF3) on the bases of MNDO MO calcns. and linear regression analyses. The QSAR analyses indicate the following characteristic for the inhibitory activity of 2-sulfinylbenzimidazoles: the attack of pyridine nitrogen to 2-position of benzimidazole moiety is the most important step of the rearrangements to interact with (H+,**K**+)-**ATPase**.

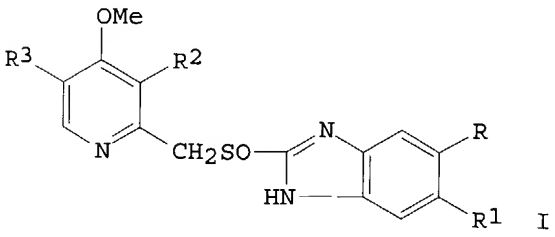
L4 ANSWER 51 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:601 CAPLUS
DN 118:601
TI Ultrastructural investigations of the enterochromaffin-like (ECL) cells in three different rat strains (Sprague-Dawley, Fischer 344, Wistar) after treatment with the H+,**K+-ATPase** inhibitor pantoprazole
AU Rohr, I.; Ockert, D.; Reznik, G. K.
CS Inst. Pathol. Toxicol., Byk Gulden Pharm., Hamburg, W-2000/70, Germany
SO Experimental and Toxicologic Pathology (1992), 44(4), 197-200
CODEN: ETPAEK; ISSN: 0940-2993
DT Journal
LA English
AB All 3 title strains of rats showed close conformity of fundic ECL cell d. and morphol. Treatment with pantoprazole increased serum gastrin concentration and the d. of gastrin-producing cells in all the strains, but the electron-microscopically determined d. of ECL cells was markedly increased in the Sprague-Dawley strain only. Ultrastructurally, the treated rats showed activation of the ECL cells and enhanced histamine release. The Sprague-Dawley and Fischer strains had an enhanced proportion of large ECL cell granules, with the Fischer rats also showing an increased granule d. In contrast, the treated Wistar rats had a lower granule d. and a higher proportion of small- and medium-sized granules than did the control Wistar rats.

L4 ANSWER 52 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:563647 CAPLUS
DN 117:163647
TI Pantoprazole: a novel hydrogen ion/potassium-ATPase inhibitor with an improved pH stability
AU Beil, W.; Staar, U.; Sewing, K. F.
CS Inst. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, D-3000/61, Germany
SO European Journal of Pharmacology (1992), 218(2-3), 265-71
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The action of the H+/**K+-ATPase** inhibitors pantoprazole and omeprazole was compared in different in vitro test systems. In gastric membrane vesicles under conditions shown to result in acidification of the vesicle interior, pantoprazole and omeprazole inhibited H+/**K+-ATPase** activity with IC50 values of 6.8 and 2.4 μM, resp. When intravesicular acidification was reduced by inclusion of imidazole (5 mM), a membrane permeable weak base, the inhibitory action of omeprazole was partially lost (IC50 30 μM) and that of pantoprazole almost completely lost. After incubation for 40 min with pumping membrane vesicles, a half-maximal reduction in intravesicular H+ concentration occurred at pantoprazole and omeprazole concns. of 1.1 and 0.6 μM, resp. Again, when the intravesicular H+ concentration was reduced by inclusion of imidazole (2.5 mM), pantoprazole (20 and 60 μM) did not reduce the remaining intravesicular proton concentration, whereas omeprazole (10 and 30 μM) did. Both drugs inhibited, with similar potency, papain activity at pH 3.0 and inactivated the enzyme in a similar time-dependent manner; at pH 5.0 omeprazole (IC50 17 μM) was more potent than pantoprazole (IC50 37 μM) and enzyme inhibition was faster than with pantoprazole. These results indicate that pantoprazole is a potent inhibitor of H+/**K+-ATPase** under highly acidic conditions and that it is more stable than omeprazole at a slightly acidic pH such as pH 5.0.

L4 ANSWER 53 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1992:503984 CAPLUS
DN 117:103984
TI Effects of oral pantoprazole on 24-hour intragastric acidity and plasma gastrin profiles
AU Hannan, A.; Weil, J.; Broom, C.; Walt, R. P.
CS Univ. Dep. Med., Queen Elizabeth Hosp., Birmingham, B15 2TH, UK
SO Alimentary Pharmacology and Therapeutics (1992), 6(3), 373-80
CODEN: APTHEN; ISSN: 0269-2813
DT Journal
LA English
AB Pantoprazole selectively blocks gastric parietal cell H+,**K**+-**ATPase**. To define a dosage regimen for clin. trials, the authors compared the effect of pantoprazole 40 and 60 mg daily on 24-h intragastric acidity and plasma gastrin concns. using a double-blind, randomized, cross-over design. Eleven men took each of the three regimens (placebo, 40, 60 mg) for 5 days. On Day 5, 24-h pH metry and plasma gastrin profile were performed. A consistent decrease in intragastric acidity with each dosage regimen was shown by a rise in 24-h median pH from 1.4 on placebo to 2.3 during pantoprazole 40 mg and to 3.5 during 60 mg. Pantoprazole 40 and 60 mg maintained the intragastric pH above 3 for 33% and 58% of time, resp., compared with 15% time with placebo. Twenty-four-hour integrated plasma gastrin concentration rose from 478 to 1798 and 1962 pmol·h/L, resp. The drug was well tolerated. The decrease of acidity was dose related and should result in clin. efficacy similar to other antisecretory drugs. It is not known whether higher doses might abolish acid secretion. The optimal dose of pantoprazole is yet to be established.

L4 ANSWER 54 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:151648 CAPLUS
DN 116:151648
TI (H+, **K**+)-**ATPase** inhibiting 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles. 4. A novel series of dimethoxypyridyl-substituted inhibitors with enhanced selectivity. The selection of pantoprazole as a clinical candidate
AU Kohl, Bernhard; Sturm, Ernst; Senn-Bilfinger, Joerg; Simon, W. Alexander; Krueger, Uwe; Schaefer, Hartmann; Rainer, Georg; Figala, Volker; Klemm, Kurt; et al.
CS Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Journal of Medicinal Chemistry (1992), 35(6), 1049-57
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI



I

AB [(Pyridylmethyl)sulfinyl]benzimidazoles I (R = OCF2H, OCH2CF3, OCF2CF2H; R1 = H, OMe; RR1 = OCF2O; R2, R3 = H, Me, OMe) were prepared and tested for (H+,**K**+)-**ATPase** inhibitory activity. The aim of this study was to identify compds. with high (H+,**K**+)-**ATPase** inhibitory activity in stimulated gastric glands possessing acidic pH, but

low reactivity (high chemical stability) at neutral pH as reflected by in vitro (Na+,**K+**)-**ATPase** inhibitory activity. The critical influence of substituents flanking the pyridine 4-MeO substituent present in all derivs. was carefully studied. The introduction of a 3-MeO group gave inhibitors possessing a combination of high potency, similar to omeprazole and lansoprazole, but increased stability. As a result I (R = OCF2H, R1 = R3 = H, R2 = OMe; pantoprazole) was selected as a candidate drug and is currently undergoing phase III clin. studies.

L4 ANSWER 55 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:33946 CAPLUS
DN 116:33946
TI Lack of influence of pantoprazole on the disposition kinetics of theophylline in man
AU Schulz, H. U.; Hartmann, M.; Steinijans, V. W.; Huber, R.; Luehrmann, B.; Bliesath, H.; Wurst, W.
CS Dep. Angiol. Geriatr., Med. Univ. Luebeck, Luebeck, W-2400/1, Germany
SO International Journal of Clinical Pharmacology, Therapy and Toxicology (1991), 29(9), 369-75
CODEN: IJCPB5; ISSN: 0300-9718
DT Journal
LA English
AB The potential influence of pantoprazole (BY1023/SK&F96022), a newly developed selective inhibitor of the gastric H+, **K+-ATPase**, on therapeutic serum theophylline concns. was investigated in a crossover study in 8 healthy male volunteers. Pantoprazole was well tolerated with and without theophylline. There were no clin. relevant changes in blood pressure, heart rate, ECG and routine clin. laboratory parameters. Primary characteristic for confirmative assessment of no interaction was the area under the concentration/time curve (AUC). Lack of interaction in the sense of equivalence was concluded both for theophylline (with and without pantoprazole) and pantoprazole (with and without theophylline), as the 90%-confidence intervals of the AUC-ratio test/reference were within the equivalence range of 0.8 to 1.25. Further explorative anal. of theophylline disposition kinetics revealed this inclusion also for clearance and volume of distribution, but not for the half-life. In the case of pantoprazole, the corresponding 90%-confidence intervals for any of the secondary characteristics clearance, volume of distribution and half-life were within the above mentioned range. In conclusion, repeated once-daily i.v. injections of 30 mg pantoprazole have no clin. relevant influence on steady-state theophylline serum concns., nor does theophylline at therapeutic serum concns. influence the pantoprazole disposition kinetics. Hence, in clin. practice theophylline and pantoprazole can be administered concomitantly without dose adjustment.

L4 ANSWER 56 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:622796 CAPLUS
DN 115:222796
TI The hydrogen ion-potassium APTase inhibitor pantoprazole (BY1023/SK&F96022) interacts less with cytochrome P450 than omeprazole and lansoprazole
AU Simon, W. Alexander; Buedingen, Christian; Fahr, Susanne; Kinder, Burkhard; Koske, Marga
CS Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Biochemical Pharmacology (1991), 42(2), 347-55
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The gastric acid antisecretory compound omeprazole, a member of the new class of H+,**K+-ATPase** inhibitors, is known to interact with the metabolism of other drugs in vitro and in vivo. In this study, two

other substituted benzimidazoles, pantoprazole and lansoprazole are compared for their ability to inhibit cytochrome P 450 dependent biotransformation in vitro with regard to three representative reactions: O-dealkylation of 7-ethoxycoumarin (EC), N-demethylation of ethylmorphine (EM) and hydroxylation of lonazolac (Lona). These reactions can be seen in microsomes from phenobarbital pretreated rats representing the cytochrome P450IIB1 subfamily. As shown in presence of known inhibitors of cytochrome P 450, e.g. SK&F 525A, metyrapone, chlorpromazine and nitrendipine, different enzymes seem to be responsible for these three indicator reactions of the cytochrome P450IIB1 complex. These reactions are inhibited to a different extent by the three H+,**K**+-**ATPase** inhibitors. Pantoprazole shows the lowest inhibitory activity vs. the three reactions (Ki, μmol/L): EC, 138; EM, 104; Lona, 128. A greater effect is observed with omeprazole: EC, 38; EM, 68; Lona, 20. Lansoprazole exceeds omeprazole in inhibiting the three cytochrome P 450-dependent enzymes: EC, 17; EM, 34; Lona, 8. In microsomes from untreated rats with the predominant cytochrome P450IIA1 subfamily as well as in microsomes from isopropanol treated rats (induction of cytochrome P450IIE1) which catalyze only lonazolac hydroxylation to a detectable amount, the latter reaction was inhibited by pantoprazole with a somewhat lower Ki of 77 whereas the values for omeprazole and lansoprazole remained unchanged in comparison to those found in microsomes from phenobarbital pretreated rats. The biotransformation rate of the substituted benzimidazoles themselves in microsomes from control and induced rats is lowest for pantoprazole followed by lansoprazole and omeprazole.

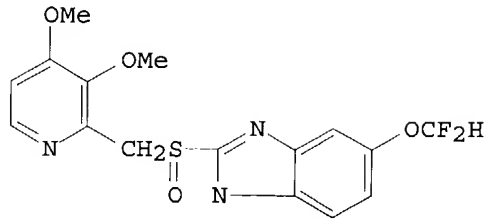
L4 ANSWER 57 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:598167 CAPLUS
DN 115:198167
TI The novel proton pump inhibitor pantoprazole elevates intragastric pH for a prolonged period when administered under conditions of stimulated gastric acid secretion in the gastric fistula dog
AU Postius, S.; Braeuer, U.; Kromer, W.
CS Dep. Pharmacol., Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Life Sciences (1991), 49(14), 1047-52
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB The duration of intragastric pH-elevation upon administration of the novel H+**K**+-**ATPase** inhibitor pantoprazole and its pharmacodynamic interaction with H2 receptor blockade was assessed in the gastric fistula dog using the intragastric 24 h pH-metry. Gastric acid secretion was stimulated by s.c. pentagastrin infusion. Group A received i.v. saline (controls), group B once an i.v. bolus of pantoprazole and group C twice the H2-receptor antagonist famotidine. Group D received the doses of famotidine and pantoprazole used in groups B and C. The intragastric pH-elevating effect of pantoprazole was not prolonged but, in fact, shortened by the pretreatment with famotidine. Moreover, this effect depended on the pretreatment-dose of famotidine. The results indicate that substituted benzimidazoles like pantoprazole need to be chemical activated in the acidic compartment of the parietal cell to produce a sustained intragastric pH-elevation. With regard to the potential therapeutic implication of these observations it is speculated that pantoprazole may be most effective in patients with high gastric acid secretion but may display reduced duration of intragastric pH-elevation under conditions of low acid secretion when acid blockade is not required.

L4 ANSWER 58 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:400183 CAPLUS
DN 115:183
TI In vivo cytochrome P 450 interactions of the newly developed hydrogen ion, potassium-ATPase inhibitor pantoprazole (BY 1023/SK and F 96022) compared

to other antiulcer drugs
AU Hanauer, G.; Graf, U.; Meissner, T.
CS Dep. Pharmacol., Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Methods and Findings in Experimental and Clinical Pharmacology (1991), 13(1), 63-7
CODEN: MFEPDX; ISSN: 0379-0355
DT Journal
LA English
AB The aim of the present study was to investigate in vivo interactions of the H2-blocker cimetidine and three newly developed H+/**K**+-**ATPase** inhibitors, omeprazole, lansoprazole and pantoprazole (BY 1023/SK&F 96022) with cytochrome P 450 in rats. Because diazepam is a drug used very often as comedication in ulcer patients, the duration of the effects of diazepam on muscle coordination were used to evaluate the drug interactions with metabolic enzymes. The present data indicate a clear rank order of the antiulcer drugs potency for interaction with diazepam: 1) lansoprazole with a 50% prolongation of diazepam effect at 170 μmol/kg. 2 cimetidine and omeprazole at 281 and 288 μmol/kg, resp. and 3) pantoprazole at >1000 μmol/kg. Because of three H+/**K**+-**ATPase** inhibitors are approx. equipotent with respect to inhibition of gastric acid secretion, it can be concluded that pantoprazole is superior to omeprazole and lansoprazole when unwanted adverse effects on drug-metabolizing enzymes are considered. This may be an advantage in clin. use of the drug.

L4 ANSWER 59 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:445 CAPLUS
DN 114:445
TI Direct comparison between the ulcer-healing effects of two hydrogen ion, potassium-ATPase inhibitors, one M1-selective antimuscarinic and one H2 receptor antagonist in the rat
AU Kromer, W.; Goenne, S.; Riedel, R.; Postius, S.
CS Dep. Pharmacol., Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Pharmacology (1990), 41(6), 333-7
CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
AB A direct comparison of the ulcer-healing effects of two H+-**K**+-**ATPase** inhibitors (pantoprazole and omeprazole), one M1 antimuscarinic (telenzepine) and one H2 receptor antagonist (cimetidine) was performed in the rat. Gastric and duodenal ulcers were induced by local application of acetic acid and thereafter treated over 10 days by the test drugs. Overall and on a molar basis, ulcer healing was comparably accelerated by pantoprazole, omeprazole and telenzepine and less so by cimetidine. The same rank order was found with respect to the inhibition of gastric acid secretion in the modified Shay rat.

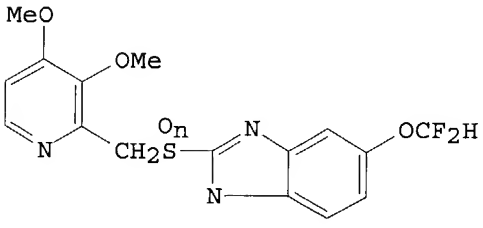
L4 ANSWER 60 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:565222 CAPLUS
DN 113:165222
TI Single intravenous administration of the hydrogen,potassium-ATPase inhibitor BY 1023/SKF 96022-inhibition of pentagastrin-stimulated gastric acid secretion and pharmacokinetics in man
AU Simon, B.; Mueller, P.; Bliesath, H.; Luehmann, R.; Hartmann, M.; Huber, R.; Wurst, W.
CS Krankenhaus Schwetzingen, Schwetzingen, 6830, Germany
SO Alimentary Pharmacology and Therapeutics (1990), 4(3), 239-45
CODEN: APTHEN; ISSN: 0269-2813
DT Journal
LA English
GI



I

AB The effects of the H+,**K+-ATPase** inhibitor BY 1023/SKF 96022 (I) on pentagastrin-stimulated acid secretion have been studied in healthy male volunteers. The gastric acid response to submaximal pentagastrin-stimulation (0.6 μg/h/kg) was dose-dependently inhibited. A single dose of 5 mg decreased acid output by 22% while after 60 and 80 mg secretion was almost completely abolished. A good dose linearity was observed for AUC and Cmax over the dose range from 5 to 80 mg. Elimination half-life, total clearance and volume of distribution of the parent compound were independent of the dose. The drug was well tolerated up to the highest dose of 80 mg. No clin. relevant influence was found on either laboratory screen or cardiovascular parameters.

L4 ANSWER 61 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:564847 CAPLUS
DN 113:164847
TI High-performance liquid chromatographic determination of the hydrogen ion/potassium ATPase inhibitor (BY 1023/SK&F96 022) and its sulfone metabolite in serum or plasma by direct injection and fully automated pre-column sample clean-up
AU Huber, R.; Mueller, W.; Banks, M. C.; Rogers, S. J.; Norwood, P. C.; Doyle, E.
CS Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Journal of Chromatography (1990), 529(2), 389-401
CODEN: JOCRAM; ISSN: 0021-9673
DT Journal
LA English
GI



I, n=1

II, n=2

AB A fully automated HPLC method is described for the determination of the new H+/**K+ ATPase** inhibitor BY 1023/SK&F 96022 (I) and its major metabolite (II) occurring in dog serum. The method uses direct sample injection of up to 200 μL and a pre-column switching technique. In order to optimize the recovery, pre-column conditions were varied systematically with resp. to the pH of the pre-column eluent, its buffering capacity and content of acetonitrile. Optimization resulted in near 100% recovery for both compds., thus allowing the use of external standardization. The linearity range, precision and detection limits were determined and the method shown to be applicable to both serum and plasma. The

method was applied to define the pharmacokinetics in dogs and humans.

L4 ANSWER 62 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:509083 CAPLUS
DN 113:109083
TI BY 1023/SK&F 96022 INN pantoprazole, a novel gastric proton pump inhibitor, potently inhibits acid secretion but lacks relevant cytochrome P450 interactions
AU Kromer, W.; Postius, S.; Riedel, R.; Simon, W. A.; Hanauer, G.; Brand, U.; Goenne, S.; Parsons, M. E.
CS Byk Gulden Pharm., Konstanz, D-7750, Germany
SO Journal of Pharmacology and Experimental Therapeutics (1990), 254(1), 129-35
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The novel H+/**K**+-**ATPase** inhibitor (gastric proton pump inhibitor) BY1023/SK&F 96022, was found to be more potent than omeprazole in some rat models and slightly less potent in a dog model. Overall, both compds. are of a similar potency and efficacy. BY 1023/SK&F 96022 exhibited a somewhat longer duration of the antisecretory action than omeprazole in the Ghosh-Schild rat. In the modified Shay rat, on the basis of equieffective doses in terms of the initial effect, both compds. had a comparable duration of action. However, the oral/i.v. dose ratio upon acute administration was larger for omeprazole, possibly reflecting its lower stability in the acidic environment of the secreting stomach, compared to BY 1023/SK&F 96022. As in vivo, both compds. were equipotent to inhibit acid production in rabbit isolated fundic glands. However, omeprazole interacted with 7-ethoxycoumarin dealkylase in vitro with high affinity in contrast to BY 1023/SK&F 96022. Compared to omeprazole, BY 1023/SK&F 96022 also showed less interaction with the cytochrome P 450 enzyme hydroxylation lonazolac. Moreover, this difference between the two compds. was also found in the rat in vivo with resp. to their interaction with diazepam. Thus both compds. displayed a comparable antisecretory potency in vivo and in vitro but showed a different interference with cytochrome P 450 in favor of less interaction by BY 1023/SK&F 96022.

L4 ANSWER 63 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:471057 CAPLUS
DN 113:71057
TI BY 1023/SK&F 96022: biochemistry of a novel (hydrogen ion-potassium) ATPase inhibitor
AU Simon, W. Alexander; Keeling, David J.; Laing, Shiona M.; Fallowfield, Colin; Taylor, Amanda G.
CS Smith Kline and French Res. Ltd., Welwyn/Herts., AL6 9AR, UK
SO Biochemical Pharmacology (1990), 39(11), 1799-806
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The mechanism by which the substituted benzimidazole sulfoxide BY 1023/SK&F 96022 inhibited the (H+ + **K**+)-**ATPase**, the enzyme responsible for hydrogen ion secretion in the stomach, was studied in a variety of in vitro prepns. In gastric prepns. that were capable of active hydrogen ion transport with consequent lumenal acidification, BY 1023/SK&F 96022 inhibited with high potency and in a time-dependent manner consistent with the acid-induced conversion of the parent benzimidazole sulfoxide to a covalent inhibitor (cyclic sulphenamide). The following IC50 values were obtained for the inhibition of aminopyrine accumulation: intact gastric glands stimulated with 1 mM dibutyryl cAMP, 1.0μM; permeabilized gastric glands stimulated with 5 mM MgATP, 0.42 μM; intact gastric vesicles stimulated with 150 mM KCl, 9μM valinomycin and 2 mM MgATP, 3.5 μM. In a preparation that could not generate pH gradients,

lyophilized gastric vesicles at pH 7.4, BY 1023/SK&F 96022 inhibited K+-stimulated ATPase activity with relatively low potency, 70 μM, indicating its good chemical stability at neutral pH. As assessed by ATPase inhibition, this stability was three times greater than that of omeprazole. Inhibition could, however, be completely reversed by subsequent incubation with 20 mM β-mercaptoethanol (intact gastric glands) or 100 mM dithiothreitol (intact gastric glands vesicles) suggesting a disulfide link between inhibitor and enzyme. The concentration of glutathione needed to protect against inhibition by BY 1023/SK&F 96022 was 10,000 times higher in intact, compared with lyophilized, gastric vesicles indicating an interaction with the lumenal (extracellular) face of the (H+ + **K**+)-**ATPase**. BY 1023/SK&F 96022 and omeprazole were also found to inhibit acidification in purified kidney lysosomes with IC50 values of 194 and 75 μM, resp. Protection by 10 μM glutathione suggested that this did not result from intralysosomal activation of these inhibitors. Thus, BY 1023/SK&F 96022 has the combined properties of good chemical stability at neutral pH and effective conversion to the cyclic sulphenamide at acidic pH. In this way the activation to the cyclic sulphenamide may be optimally restricted to the parietal cell canaliculus.

L4 ANSWER 64 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:417379 CAPLUS
DN 113:17379
TI Two systems for the automated analysis of drugs in biological fluids using high-performance liquid chromatography
AU Doyle, E.; McDowall, R. D.; Murkitt, G. S.; Picot, V. S.; Rogers, S. J.
CS Dep. Drug Anal., Smith Kline and French Res. Ltd., Welwyn/Hertfordshire, AL6 9AR, UK
SO Journal of Chromatography (1990), 527(1), 67-77
CODEN: JOCRAM; ISSN: 0021-9673
DT Journal
LA English
AB This paper describes 2 fully automated assays. One for zaprinast, a cGMP specific phosphodiesterase inhibitor, which uses the Gilson-Advanced Automated Sample Processor combination, and the other for an H+/**K** + **ATPase** inhibitor and it sulfone metabolite, which uses direct injection. Both assays were developed to support pharmacokinetic studies at therapeutic doses in small animals as well as in man. Plasma or serum (20-200 μL) is placed directly into an autosampler and all subsequent manipulations are performed mech.

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